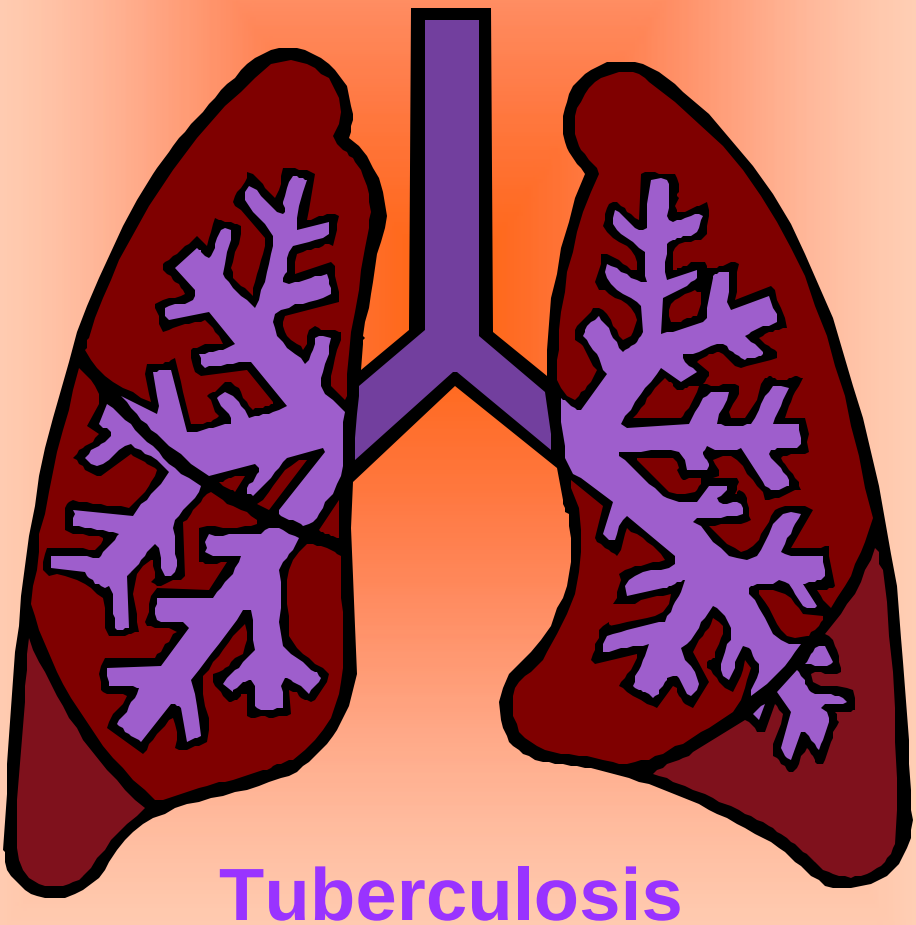
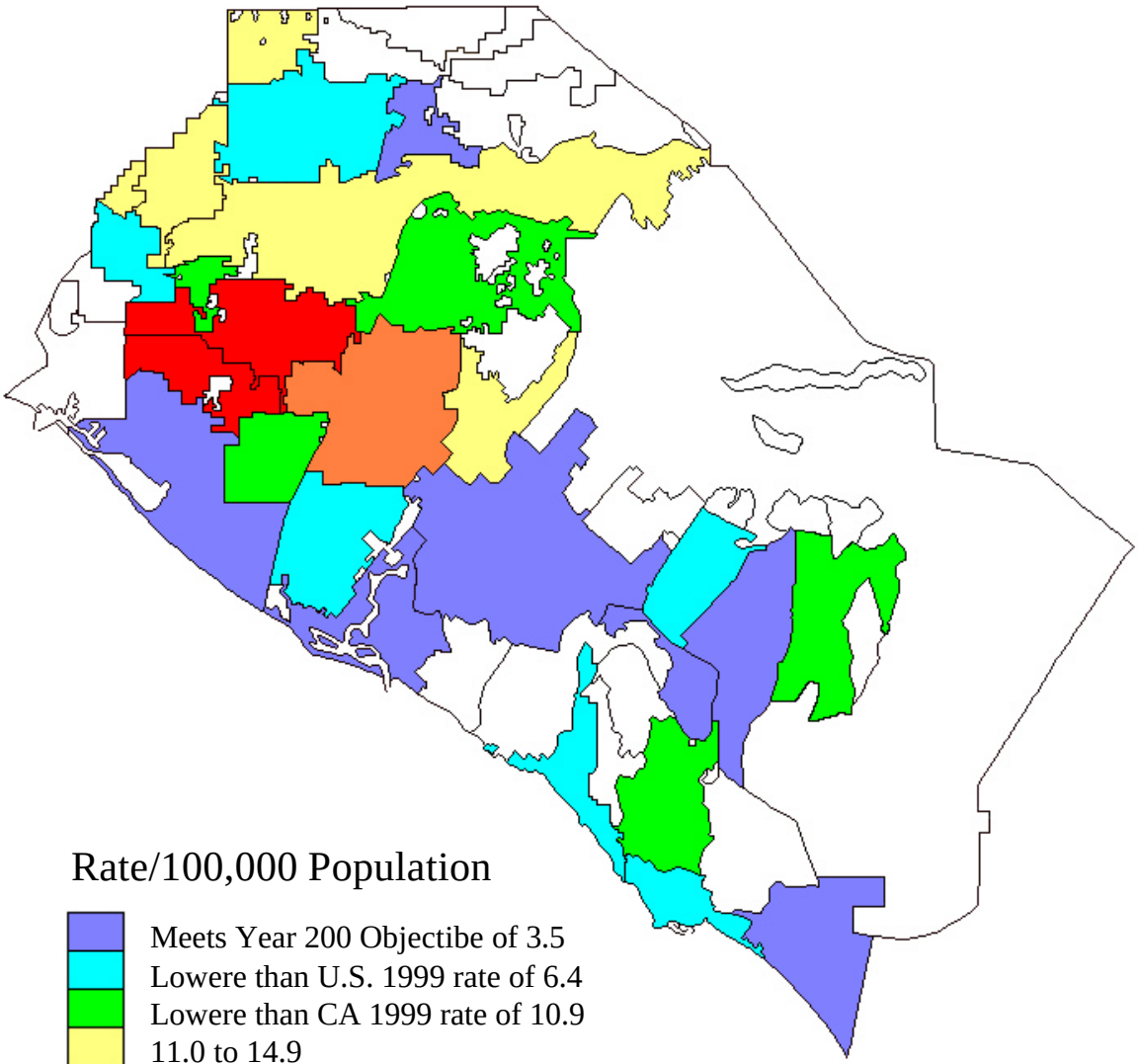
County of Orange
Health Care Agency



Tuberculosis

Policies, Protocols and Recommendations
January 2001

TB Rates by City
Orange County - 2000



Rate/100,000 Population

- Meets Year 200 Objectibe of 3.5
- Lowere than U.S. 1999 rate of 6.4
- Lowere than CA 1999 rate of 10.9
- 11.0 to 14.9
- 15.0 to 20.9
- 21.0 or higher

Introduction

This manual describes policies, procedures and guidelines for diagnosis and treatment of tuberculosis in Orange County, California. This is the result of work by Orange County Health Care Agency Disease Control, Mitchel Abramsky, MD, Bisher Akil, MD, Kay Malkasian, MD, Frank Webster, MD and Penny Weismuller, DrPH.

In preparing this manual, we used sample protocols from New York City, San Francisco and Los Angeles. We updated our previous manual, and expanded the section on tuberculosis in HIV infection. We were assisted by the Centers for Disease Control and Public Health Services guidelines.

Treatment for tuberculosis continues to evolve, and opinions differ regarding many issues in the treatment. These guidelines are not meant to substitute for sound medical judgement. The treating physicians and clinicians are encouraged to seek consultation at all times.

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Classification System for TB

Class	Type	Description
0	No TB exposure Not infected	No history of exposure Negative reaction to tuberculin skin test
I	TB exposure No evidence of infection	History of exposure Negative reaction to tuberculin skin test
II	TB infection No Disease	Positive reaction to tuberculin skin test Negative bacteriologic studies (if done) No clinical or radiographic evidence of TB
III	Current TB disease	*M. tuberculosis* cultured (if done) or Positive reaction to tuberculin skin test and Clinical or radiographic evidence of current disease
IV	Previous TB disease	History of episode(s) of TB or Abnormal but stable radiographic findings Positive reaction to the tuberculin skin test Negative bacteriologic studies (if done) and No clinical or radiographic evidence of current disease
V	TB suspected	Diagnosis pending

Source: Centers for Disease Control and Prevention. Diagnostic Standards and Classification of Tuberculosis. *Amer Rev Resp Dis* 1990; 142:725-735.

I. Tuberculin Skin Testing

Contents

I.A. Candidates for Tuberculin Skin Testing

The Mantoux tuberculin skin test (TST), also known as the Mantoux purified protein derivative (PPD) test, is used to diagnose TB infection. TST screening should be focused on populations most at risk for infection. In general, populations at low risk for TB infection should not be skin tested because many reactions in such populations will be falsely positive. Tuberculin skin testing is not necessary for individuals with a documented previous positive Mantoux TST result.

1. PRIORITIES FOR TESTING

In order of priority, the following individuals should be screened for TB infection using the Mantoux TST:

1. Contacts to persons with pulmonary or laryngeal TB disease (see Section VIII) or to a child under five years of age with a positive skin test

2. Persons with HIV infection

3. Persons with other medical risk factors for TB disease, such as diabetes mellitus, silicosis, prolonged corticosteroid therapy, other immunosuppressive therapy, cancer of the head and neck, hematologic and reticuloendothelial disease (e.g., leukemia and Hodgkin's disease), end-stage renal disease, intestinal bypass or gastrectomy, chronic malabsorption syndromes, or low body weight (10% or more below ideal)

4. Persons with radiographic evidence of old, healed TB

5. Employees or residents of congregate settings, such as hospitals, correctional facilities, homeless shelters, nursing homes, or drug treatment centers

6. Persons from an area of the world where the incidence of TB is high (see Appendix A)

7. Persons needing tuberculosis clearance for employment, school, volunteer work, etc. (Fee may apply)

In addition, the TST is valuable as a diagnostic tool in patients who have symptoms and/or clinical evidence, radiographic evidence, or acid-fast bacilli smears suggestive of TB disease. In these patients, a positive TST reaction indicates TB infection and supports a diagnosis of TB disease. A negative reaction usually, but not always, excludes TB as a cause. However, immunosuppression and other medical conditions, including severe TB disease itself, can cause a false-negative reaction to the TST.

2. SKIN TESTING OF PREGNANT WOMEN

Tuberculin skin testing is safe and reliable for pregnant women; no teratogenic effects have been documented. Routine TST screening among pregnant women is not indicated because pregnancy itself does not increase the risk for TB infection. However, pregnant women at high risk for TB infection or disease should be tested. Specifically, pregnant women should be screened for TB infection if they have any of the following conditions:

- Symptoms suggestive of TB disease

- HIV infection

- Behavioral risk factors for HIV (in women who decline HIV testing)

- Medical conditions other than HIV infection that increase the risk for TB disease, such as diabetes mellitus, silicosis, prolonged corticosteroid therapy, other immunosuppressive therapy, cancer of the head and neck, hematologic and reticuloendothelial disease (e.g., leukemia and Hodgkin's disease), end-stage renal disease, intestinal bypass or gastrectomy, chronic malabsorption syndromes, or low body weight (10% or more below ideal)

- Close contact with a person who has pulmonary or laryngeal TB disease

- Immigration from an area of the world where the incidence of TB is high (see Appendix A)

For guidelines on follow-up, including chest x-rays, for TST-positive pregnant women, see Section II-A(2)

I.B. Administering the Tuberculin Skin Test

The Tuberculin skin test (TST) should be administered by the Mantoux technique, in which PPD tuberculin is injected intradermally with a needle and syringe. Multiple-puncture tests (e.g., the Tine test) should not be used, even in infants and children, because this type of test is much less accurate than a properly administered Mantoux test.

The following procedure should be used to administer a TST by the Mantoux technique:

Introduce 0.1 ml of tuberculin (5 tuberculin units) just under the top layer of skin on the forearm. Use a short, disposable, 26-gauge needle, with the needle bevel facing upward. This should cause a discrete skin elevation (a wheal) 6 to 10 mm in diameter.

Follow infection control procedures for all injections. When water is not available for hand washing, use an appropriate skin-cleaning product (e.g., antibacterial towelette).

After administering the TST, instruct the patient not to rub, scratch, or put a band-aid on the test site. The area may be washed and patted dry.

Vaccination with measles, mumps, and/or rubella (MMR) can cause a false-negative reaction to the TST. Therefore, the TST should be administered on the same day as, or at least 4 weeks after, MMR vaccine is given.

I.C. Reading the Tuberculin Skin Test Reaction

The test result should be read only by a trained health worker; patients should never be allowed to read their own reaction. The following procedure should be used to read the reaction:

- Read the result 48 to 72 hours after administering the test

- Measure only the hard, swollen area known as induration. Do not measure any redness; redness does not necessarily indicate TB infection

Measure the induration transversely at its widest point using a flexible ruler. Record the size of the induration in millimeters, not simply as "positive" or "negative." If there is no induration, record the result as "00 mm." (If the measurement is larger along the longitudinal axis, record this measurement instead of the transverse measurement.)

If the patient fails to return for the scheduled reading but returns up to a week after the test administration, examine the test site and measure any induration present. If it is large enough to be classified as positive, record the result; no repeat skin testing is needed. If there is no reaction or it is too small to be classified as positive, repeat the test.

I.D. Classifying the Tuberculin Skin Test Reaction

Whether a reaction to the Mantoux TST is classified as positive depends on the size of the induration and the person's medical and epidemiologic risk factors for TB.

≥5 mm of induration is considered positive for the following individuals:

- HIV-seropositive persons
- Persons with behavioral risk factors for HIV infection who decline HIV testing, including persons of unknown HIV status who have a history of drug injection
- Close contacts of a person who has pulmonary or laryngeal TB disease
- Persons with radiographic evidence of old, healed TB

≥ 10 mm is considered positive for all other individuals.

Patients who have a positive TST reaction should receive a clinical evaluation, including a chest x-ray, to rule out TB disease (see Sections II-A and III). If the initial chest x-ray is normal, repeated chest x-rays are not indicated unless the individual develops signs or symptoms of TB disease. TST-positive individuals should be evaluated for preventive treatment according to the guidelines in Section II-B.

I.E. Tuberculin Skin Testing of BCG-Vaccinated Individuals

BCG, or bacille Calmette-Guérin, is a vaccine used in many countries because it is believed to protect children against some forms of TB disease. However, its efficacy in preventing TB in adults is variable and controversial. TST-positive persons from countries where TB is common are likely to be TB infected and are at risk of developing TB disease, even if they have been BCG vaccinated.

BCG vaccination complicates the interpretation of TST results because it can produce a false-positive reaction to the TST, especially if BCG was given after the age of 1 year. (BCG given only at birth does not appear to be a significant cause of false-positive TST reactions.) There is no way to distinguish between a positive reaction due to BCG vaccination and a positive reaction due to true TB infection. In BCG-vaccinated persons, however, sensitivity to tuberculin is highly variable and tends to wane over time.

In general, a history of vaccination with BCG should not influence the need for tuberculin skin testing, the interpretation of the TST reaction, or clinical decisions regarding the management of TST-positive individuals.

- Patients who are close contacts of an individual with pulmonary or laryngeal TB disease are considered TST positive if they have a reaction of ≥5 mm, regardless of their BCG status. TST-positive contacts are candidates for preventive therapy (see Section II-B).
- Patients who have no other risk factors are considered TST positive if they have a reaction of ≥10 mm, regardless of their BCG status.

I.F. Anergy Testing

1. CAUSES OF ANERGY

Anergy is the inability to mount a delayed-type, cutaneous, cellular immune response. Patients who are anergic may have a negative TST reaction even if they have TB infection.

The following conditions are common causes of anergy:

- HIV infection or AIDS
- Prolonged therapy with adrenocorticosteroids, defined as more than 15 mg per day of prednisone (or equivalent) given for at least 2 to 3 weeks (there is little information about anergy in persons taking less than 15 mg per day of prednisone or the equivalent, or in persons taking corticosteroids every other day)
- Other immunosuppressive therapy, such as chemotherapy for cancer
- Some hematologic and reticuloendothelial diseases, such as leukemia, lymphoma, or Hodgkin's disease
- End-stage renal disease
- Clinical situations associated with substantial rapid weight loss or chronic under-nutrition
- Overwhelming TB disease
- Extremes of age (newborn or elderly)
- Physiologic stress, such as surgery or burns
- Certain viral infections (measles, mumps, chicken pox) or bacterial infections (typhoid fever, pertussis, brucellosis, Hansen's Disease [leprosy])
- Sarcoidosis
- Live-virus vaccinations, including MMR vaccination

2. ROLE OF ANERGY TESTING

Testing with common delayed-type hypersensitivity antigens, such as *Candida*, mumps, or tetanus, may be done to evaluate whether a person is anergic. However, anergy testing is not standardized, and its results should never be used to justify withholding preventive treatment from a person in whom it is indicated. Ultimately, a person's general risk for TB infection is more important in making decisions about preventive treatment than the results of anergy testing.

Anergy testing has no role in the evaluation of contacts. In general, TST-negative, HIV-infected close contacts of a person with pulmonary or laryngeal TB should receive preventive therapy, whether or not they are anergic. TST- negative, HIV-infected individuals who are not known to be contacts should be evaluated for preventive treatment according to their risk for TB exposure and infection.

Similarly, signs and symptoms of TB disease should take precedence over the results of anergy testing in making decisions about treatment. It is possible for a non-anergic individual to be TST negative and have TB disease.

In selected situations, however, anergy testing may be useful for the diagnosis of TB disease or infection. For example, in an elderly patient who has an equivocal chest x-ray and negative reactions to both TSTs in a two-step test, the results of anergy testing can be used to support or rule out a diagnosis of old TB (Class IV). If the patient responds to at least 1 antigen, a diagnosis of old TB is less likely. If the patient is anergic, however, a diagnosis of old TB cannot be ruled out.

3. ADMINISTERING AND READING THE ANERGY PANEL

An anergy panel is the intradermal injection of delayed-type hypersensitivity antigens, such as mumps skin test antigen (MSTA), *Candida* (Candidin®, Allermed Labs) or tetanus toxoid (fluid). Physicians may order anergy testing and other individuals authorized by Pulmonary Disease Services, physicians, registered nurses, and clinic staff who are certified in anergy testing may perform anergy testing.

The following procedure should be used to administer an anergy panel:

- Use *Candida* and mumps skin test antigens for anergy testing. However, do not use mumps skin test antigen in patients with a history of allergy to eggs or egg products. In this situation, substitute tetanus toxoid if it is not contraindicated.

- Use the Mantoux technique; do not use multiple-prong tests for anergy testing.

- Inject 0.1 ml of each antigen on the volar surface of the arm not used for the TST, in alphabetical order: *Candida*, then MSTA or tetanus toxoid, from proximal to distal (starting near the elbow and ending towards the wrist). Allow 4 to 5 cm between injection sites, and use a new, disposable needle and syringe for each injection.

- Follow infection control procedures for all injections. When water is not available for hand washing, use an appropriate skin-cleaning product (e.g., antibacterial towelette).

- At 48 to 72 hours, record the size of induration (hardness) in millimeters. Do not record the result as "positive" or "negative."

- For anergy antigens, an induration of $\geq$3 mm is considered positive. Thus, individuals with a reaction of $\geq$3 mm to any anergy antigen should be classified as not anergic. Those with a reaction of <3 mm to all anergy antigens should be classified as anergic.

I.G. Two-Step Tuberculin Skin Testing

1. BACKGROUND

In some TB-infected individuals, the ability to react to a TST diminishes over time. Thus, infected individuals who are skin tested many years after infection may have a negative TST reaction. However, if retested within the next year, they may have a positive reaction. This phenomenon, called the booster phenomenon, happens because the first TST "boosted" the immune response that had diminished over the years. Boosting is most common in persons aged 55 and older, and can also occur in BCG-vaccinated persons. However, repeated tuberculin skin testing itself does not boost reactions in individuals without TB infection or BCG vaccination.

The booster phenomenon can complicate the interpretation of TST results in settings where testing is done repeatedly, because a boosted reaction to a second TST may be mistaken for a recent conversion. Thus, an infection acquired years ago may be interpreted as recent infection.

To eliminate boosted reactions as a cause of confusion, individuals who will be tuberculin skin tested repeatedly should undergo two-step testing the first time that they are tested. With this type of testing, an initial TST is done; if the result is negative, a second TST is given 1 to 3 weeks later. The result of the second test is then used as the baseline. If it is positive, the patient is considered infected; if negative, the patient is considered uninfected.

2. CANDIDATES AND PROCEDURE FOR TWO-STEP TESTING

Two-step testing should be offered to individuals who cannot document a history of a negative TST reaction within the past year and who will be tested repeatedly, such as health care workers and employees or residents of congregate settings. The procedure is as follows:

- If the reaction to the initial TST is negative, repeat the TST in 1 to 3 weeks, using the same dose and strength of tuberculin. Inject the tuberculin on the other forearm or at least 5 cm away from the original test site

- If the reaction to the second TST is negative (see Section I-D), classify the individual as uninfected (TB Class 0 or TB Class I)

- If the reaction to the second TST is positive (see Section I-D), obtain a chest x-ray. If the chest x-ray is abnormal, classify the individual as TB Suspect (Class V) and evaluate for TB disease (see Section III) or other pulmonary disorder. **Suspected TB cases must be reported to Public Health (at (714) 834-8790) within 1 working day.** If the chest x-ray is normal, classify the individual as having TB infection (Class II) and evaluate for preventive treatment (see Sections II-A, II-B)

If the reaction to the initial TST is positive, obtain a chest x-ray. If the chest x-ray is abnormal, classify the individual as TB Suspect (Class V) and evaluate for TB disease (see Section IV) or other pulmonary disorder. **Suspected TB cases must be reported to Public Health (at (714) 834-8790) within 1 working day.** If the chest x-ray is normal, classify the individual as having TB infection (Class II) and evaluate for preventive treatment (see Sections II-A, II-B). A second TST is not necessary.

Individuals who can provide documentation of a negative reaction to a Mantoux TST given within the preceding year should be given an initial TST and classified on the basis of that result. A second TST is not necessary because the earlier test is, in effect, the first of a two-step test.

I.H. Source Case Investigation

A source case investigation should be performed surrounding all children less than 5 years of age with a positive TST reaction (even in the absence of active TB). Public Health can help with this investigation. To request help with this investigation call (714) 834-8790.

The possible source patient is usually an adult in the home, or an adult with whom the child spends significant periods of time (e.g. baby sitters, day care personnel, and relatives).

1. POSSIBLE SOURCE PATIENT WHO IS SYMPTOMATIC

Any possible source patient who has symptoms suggestive of TB should be evaluated for TB disease (see Section III), including a TST, a chest x-ray, and the collection of three consecutive daily sputum samples for AFB smear, culture, and drug susceptibility testing.

2. POSSIBLE SOURCE PATIENT WHO IS ASYMPTOMATIC

The evaluation and management of an asymptomatic possible source patient depends on his or her HIV status and risk for HIV infection.

If the possible source patient is immunocompetent and not at risk for HIV infection, he or she should be screened with a TST.

- If the TST reaction is <10 mm, the individual should be classified as uninfected with TB (Class I). No further evaluation is necessary.

- If the TST reaction is ≥10 mm, the individual should undergo a chest x-ray.

    - If the chest x-ray is normal, the individual should be classified as infected with TB (Class II). Preventive treatment should be considered if the individual is a candidate for preventive treatment (see Section II-B). Because this individual is not the source patient, the source case investigation should be continued.

    - If the chest x-ray is abnormal, the individual should be classified as TB Suspect (Class V) and evaluated for TB disease (see Section III). **Suspected TB cases must be reported to Public Health at (714) 834-8790 within 1 working day.**

If the possible source patient (1) is HIV seropositive or otherwise immunosuppressed or (2) has behavioral risk factors for HIV infection but declines HIV testing, he or she should be screened with a TST. In addition, this individual should receive a chest x-ray and a medical evaluation, regardless of the TST reaction. Preventive treatment or treatment for TB disease should be started as appropriate.

II. Treatment of Latent Tuberculosis Infection

Contents

II.A. Medical Evaluation for Treatment of Latent Tuberculosis Infection

All individuals found to have a positive tuberculin skin test (TST) reaction should be examined to rule out active tuberculosis disease and evaluated for treatment of latent tuberculosis infection (LTBI). The medical evaluation should include the following:

1. MEDICAL HISTORY AND PHYSICAL EXAMINATION

- All individuals older than 12 years, including those without behavioral risk factors for HIV, should be counseled and offered HIV testing unless they have documentation of (1) a positive HIV antibody test, or (2) a negative result to an HIV antibody test given less than 6 months ago.

- All patients should be screened for risk factors for the development of tuberculosis disease, including recent close contact with a person who has infectious TB disease.

- Patients should be asked about previous treatment for active TB disease or treatment of LTBI. Those who have completed a course of treatment in the past should be questioned about previous adverse reactions to the medication. For HIV-negative patients, a chest x-ray and a repeat course of treatment for latent TB infection are not necessary. However, HIV-infected patients who have completed a course of treatment for latent infection but who have been recently exposed to a person with infectious pulmonary or laryngeal TB should receive another course of treatment, regardless of their CD4 and T-lymphocyte count.

- All patients should be evaluated for and asked about their history of alcohol ingestion, liver disease, and hepatitis.

Active hepatitis and end-stage liver disease are contraindictions to the use of isoniazid or pyrazinamide for treatment of latent TB infection.

2. CHEST X-RAY

All individuals being considered for treatment of LTBI should undergo a chest x-ray to rule out active pulmonary TB disease. Children under the age of 5 years (i.e., up to the day of the fifth birthday) should undergo both a posterior-anterior and a lateral chest x-ray views. All other individuals should receive a posterior-anterior view only; additional x-rays should be performed at the discretion of the physician.

- Individuals with a normal chest x-ray, a positive TST reaction, and no signs or symptoms of active TB disease should be classified as Class II, and may be candidates for treatment of LTBI.

- Individuals with an abnormal chest x-ray consistent with active pulmonary or extra-pulmonary TB disease should be classified as a TB suspect, Class V, and managed according to Sections IV and V.

- Individuals with a chest x-ray showing noncalcified fibrotic lesions suggestive of previous, healed TB, should be evaluated for current symptoms of TB and three consecutive sputum samples obtained on separate days for acid fast smear, culture and susceptibility testing. Nodules and fibrotic scars may contain slowly multiplying tubercle bacilli with substantial potential for future progression to active TB.

- Calcified nodular lesions (calcified granulomas) and apical or basal pleural thickening pose a lower risk for progression to active TB.

A chest x-ray should be given immediately, even during the first trimester, to pregnant women who:

- Have symptoms highly suggestive of active TB disease (cough, fever, night sweats, chest pain, etc.), *or*
- Are HIV-infected and TST positive, or
- HIV-infected and TST positive or TST negative but have been in close contact to a person with infectious pulmonary or laryngeal TB

3. SPUTUM EXAMINATIONS

Sputum examination is not indicated for most individuals being considered for treatment of LTBI. Collection of three consecutive sputum specimens on three separate days are recommended for the following individuals:

- Chest radiograph is suspicious for active TB
- Chest radiograph shows prior, healed TB
- Individualized recommendation for chest radiograph with calcified granulomas and apical or basal pleural thickening
- HIV-infected individual who has respiratory symptoms and a normal chest radiograph

4. LABORATORY TESTING

Baseline laboratory testing is not routinely required for all patients at the start of treatment for LTBI. Patients whose initial evaluation suggests a liver disorder should have baseline liver function tests: AST (SGOT), ALT (SGPT), and bilirubin. Baseline testing is also indicated for patients with HIV-infection, pregnant women, women in the immediate postpartum period (i.e., within three months of delivery), persons with a history of chronic liver disease (e.g., hepatitis B or C, alcoholic hepatitis, or cirrhosis), persons who use alcohol regularly, and persons at risk for chronic liver disease. Individuals taking other hepatotoxic medications should also receive baseline testing. Baseline testing is not routinely recommended in older persons but may be considered on an individual basis.

II.B. Candidates for Treatment of Latent Tuberculosis Infection (LTBI)

1. INDIVIDUALS WHO SHOULD RECEIVE TREATMENT OF Latent Tuberculosis Infection

Individuals in the following categories should be considered for therapy if their tuberculin skin test is positive and they have not previously completed a course of therapy for tuberculosis or LTBI:

- HIV-infected persons, and persons with behavioral risk factors for HIV-infection who decline HIV testing, regardless of age
- Recent TST converters (10 mm or greater increase within a 2 year period) regardless of age
- Close contacts to an infectious case, regardless of age
- Children and adolescents younger than 18 years of age

- Foreign-born persons:

  Recent arrivals (within the last 5 years) from high prevalence countries, regardless of age

  Individual assessment of persons who arrived more than 5 years ago from high prevalence countries

- Residents of a high risk congregate setting

- Persons with medical risk factors associated with an increased risk for progression to active TB including:

  Injecting drug users, regardless of HIV serostatus
  Diabetes Mellitus
  Silicosis
  End-stage renal disease
  Chronic immunosuppression
    Transplant recipients
    Prolonged corticosteroid therapy (defined as receiving the equivalent of greater than or equal to 15 mg of prednisone for one month or more)
    Hematological and reticuloendothelial disease
    Other immunosuppressive therapy
  Malnutrition and clinical situations associated with rapid weight loss
    Cancer of the head and neck
    Jejunoileal bypass or gastrectomy
    Chronic malabsorbtion syndromes
    Low body weight (less than 90% of ideal body weight)

- Other individuals with a 10 mm or greater TST reaction. These individuals may be wait listed for care if necessary or referred to their private provider for treatment.

2. <u>INDIVIDUALS WHO SHOULD START TREATMENT REGARDLESS OF THEIR TST REACTION</u>

Individuals who have recently been exposed to TB may have a false-negative reaction to the TST if tested less than 12 weeks since their last exposure. These individuals should be retested 10-12 weeks after their last contact with the infectious case. During the time period between the TSTs, the following individuals should start treatment of LTBI, even if the TST is negative:

- Contacts younger than 5 years of age

- Contacts with HIV-infection, or with behavioral risk factors for HIV-infection

- Other immunosuppressed individuals

- Close contacts in circumstances that suggest a high probability of infection. For example, evaluation of other contacts with similar degree of exposure demonstrates a high prevalence of infection, documented converters, or secondary cases

If the repeat TST result is negative, and the contact is not immunosuppressed, treatment may be discontinued. For most close contacts known to have HIV-infection, or who are at risk for HIV-infection, a full course of treatment for LTBI is recommended, regardless of the TST result.

If the repeat TST is positive, treatment for LTBI should be restarted and continued for the recommended duration of treatment.

3. PREGNANT WOMEN AS CANDATES FOR TREATMENT OF LATENT TB INFECTION

In most pregnant women, treatment of LTBI should be delayed until 2-3 months after delivery, even though no harmful effects of isoniazid on the fetus have been documented. In some situations, however, treatment of LTBI should begin during pregnancy:

- Treatment of LTBI should be started in the first trimester of pregnancy for

  TST-positive (5 mm or greater) pregnant women who are HIV-infected or who have behavioral risk factors for HIV-infection but decline HIV testing

  TST-positive (5 mm or greater) pregnant women who have been in close contact with a smear-positive pulmonary TB case

- Treatment of LTBI should be started promptly for pregnant women who have had a documented TST conversion in the past two years

- Treatment of LTBI should be started after the immediate postpartum period (i.e., three months after delivery) for all other pregnant women, including those with radiographic evidence of prior, healed TB

Pregnant women known or suspected to be infected with an organism resistant to at least isoniazid and rifampin, treatment of LTBI should be delayed until after delivery and the immediate postpartum period because of possible adverse effects of the medications on the developing fetus. A chest x-ray should be obtained initially and again if the woman develops symptoms suggestive of tuberculosis disease. Pregnant women should be protected appropriately with a lead shield when chest x-rays are taken.

II.C. Regimens for the Treatment of Latent Tuberculosis Infection

Persons with LTBI who are included among those at risk for progression to active disease should be offered treatment. Before beginning treatment of LTBI, active TB should be ruled out by history, physical examination, chest radiography, and, when indicated, bacteriologic studies. Intermittent regimens, and regimens for children under the age of five, are administered as directly observed therapy (DOT).

1. ISONIAZID (INH)

Isoniazid alone may be given daily or twice weekly for 6 to 9 months.

- Six month regimen for HIV-negative adults

- Nine month regimen for HIV-positive patients, patients suspected of having HIV-infection, or patients with radiographic evidence of prior TB in whom active disease has been ruled out.

- Six to nine month regimen for pregnant women at risk for progression to active disease. For pregnant women who are HIV-positive, close contacts to an infectious case, or recent TST converters, initiation of therapy should not be delayed, even in the first trimester. Six month regimen for HIV-negative women; nine month regimen for HIV-infected women.

- Nine month regimen for children and adolescents. Isoniazid is administered to children under five years of age as directly observed therapy.

The contraindications to treatment of LTBI with isoniazid are as follows:

- History of an isoniazid-induced reaction, including hepatic, skin, other allergic reactions, or neuropathy.
- Close contact with a person who has isoniazid-resistant TB disease.
- Severe chronic liver disease
- Pregnancy, unless the woman is at risk for progression to active disease (see above). Treatment of LTBI for women at lower risk for active disease should be delayed until after the immediate postpartum period, i.e., until three months after delivery.
- Base SGOT/AST values that are 3 to 5 times the normal value, though not a contraindication for starting treatment of LTBI, require close serial monitoring of the patient's liver function tests.

2. RIFAMPIN AND PYRAZINAMIDE

Rifampin and pyrazinamide as a 2-month daily or intermittent regimen is an alternative treatment for HIV-infected and non-infected persons. Protease inhibitors or non-nucleoside reverse transcriptase inhibitors (NNRTIs) should generally not be administered concurrently with rifampin; rifabutin can be used as an alternative (see below).

- Adult patients with LTBI who cannot tolerate isoniazid or who are contacts of patients with isoniazid-resistant, rifampin-susceptible TB, rifampin and pyrazinamide given daily for two months is recommended.
- This option may be preferred in certain settings where longer treatment is not feasible, such as jails or homeless shelters.
- This short course treatment of LTBI should be directly observed.

The contraindictions to treatment of LTBI with rifampin and pyrazinamide are as follows:

- History of rifampin-induced reaction, including hepatic, skin and other allergic reactions, or thrombocytopenia
- Severe chronic liver disease
- Pregnancy
- Current treatment with a protease inhibitors or NNRTIs. In some circumstances, rifabutin may be substituted, and can safely be used with indinavir, nelfinavir, amprenavir, ritonavir, and efavirenz, but not with hard-gel saquinavir, or delaviridine. Rifabutin is not recommended for use for patients receiving multiple protease inhibitors, or protease inhibitors in combination with NNRTIs.

3. RIFAMPIN

Rifampin alone for 4 months, either daily or twice weekly. This regimen has not been studied in randomized trials so it should be reserved for those individuals who cannot tolerate INH or pyrazinamide and for children exposed to INH resistant, rifampin sensitive TB. For adults exposed to cases with mono-

resistance to INH, the 2 month regimen of rifampin and pyrazinamide is recommended.

- Twice weekly regimens must be directly observed.

The contraindictions to treatment of LTBI with rifampin are as follows:

- History of rifampin-induced reaction, including hepatic, skin and other allergic reactions, or thrombocytopenia
- Severe chronic liver disease
- Current treatment with a protease inhibitors or NNRTIs. In some circumstances, rifabutin may be substituted, and can safely be used with indinavir, nelfinavir, amprenavir, ritonavir, and efavirenz, but not with hard-gel saquinavir, or delaviridine. Rifabutin is not recommended for use for patients receiving multiple protease inhibitors, or protease inhibitors in combination with NNRTIs.

4. ALTERNATIVE REGIMENS FOR CONTACTS OF PATIENTS WITH ISONIAZID- AND RIFAMPIN-RESISTANT TUBERCULOSIS

For persons who are likely to be infected with isoniazid- and rifampin-resistant (multidrug) TB and who are at high risk for developing TB, pyrazinamide and ethambutol or pyrazinamide and a quinolone (i.e., levofloxacin, or ofloxacin) for 6-12 months are recommended. Selection of drugs should be guided by the in vitro susceptibility results of the isolate from the source case. Immunocompetent contacts may be observed or treated for at least 6 months, and immunocompromised contacts (e.g., HIV-infected persons) should be treated for 12 months.

There have been no controlled trials of treatment for LTBI with drugs other than isoniazid and rifampin. Therefore, treatment protocols for contacts of patients with isoniazid- and rifampin-resistant TB (multidrug-resistant TB, or MDRTB) are largely empirical, and all regimens must be individualized. Four general principles apply:

- TB disease must be excluded before any treatment regimen for LTBI is initiated.
- Because HIV infection is one of the strongest risk factors for the development of TB disease, all contacts aged 18 to 64 years should be strongly encouraged to undergo voluntary HIV counseling and testing.
- The drug susceptibility pattern of the source patient must be considered in the selection of the medications for the treatment regimen.
- The treatment regimen for LTBI should include two anti-TB medications to which the source patient's isolate is susceptible.

Before selecting a regimen for treatment of LTBI, clinicians should consider the contact's risk factors for MDRTB infection and disease. Contacts who are not likely to be infected with MDRTB or who are at low risk of developing TB disease may not be candidates for an alternative treatment regimen for LTBI. At least three factors should be considered:

How likely is it that the individual is newly infected?
An individual with a prior positive TST is less likely to be newly infected and is probably not a candidate for alternative treatment. In contrast, an anergic, HIV-infected spouse of an individual with MDRTB whose three children had TST conversions is highly likely to be newly infected.

How likely is the individual to develop TB disease?
Contacts are at high risk for developing TB disease if they have been recently infected, if they are infants, or if they are HIV-infected or otherwise immunosuppressed. Physicians should be aggressive in prescribing multidrug treatment to treat LTBI in these individuals.

How likely is it that the individual is infected with a strain of MDRTB?
Infectiousness of the source case. A source case who is sputum smear positive, has cavitary disease, and is coughing, is much more infectious than a case who is smear negative and not coughing. Also, a source case whose contacts had TST conversions is more infectious than a source case whose contacts did not have TST conversions.

Closeness and intensity of the MDRTB exposure. Contacts are at higher risk for infection if they have spent a prolonged period of time sharing air with a person who has MDRTB; if they were exposed in a small, enclosed, poorly ventilated area; if they were exposed during cough-inducing procedures (bronchoscopy, sputum induction, endotracheal intubation, etc.)

Contacts' risk of exposure to drug-susceptible TB. Individuals who have been exposed to several sources of TB (e.g., some health care workers) may be less likely to have been infected with a multidrug resistant strain than individuals whose only known exposure to TB was with an infectious MDRTB patient (e.g., a TST-positive infant or a mother with MDRTB).

Table II-1 summarizes the likelihood of infection with MDRTB among contacts who are thought to be newly infected.

TABLE II-1

Likelihood of Infection with MDR-TB among Contacts Who Are Thought to Be Newly Infected

Infectiousness of the Source MDR-TB Patient	Closeness and Intensity of MDR-TB Exposure	Contact's Risk of Exposure To Drug-Susceptible TB	Estimated Likelihood of Infection with MDR-TB
+	+	-	High
+	-	-	High-intermediate
-	+	-	High-intermediate
-	-	-	Intermediate
+	+	+	Intermediate
+	-	+	Low-intermediate
-	+	+	Low-intermediate
-	-	+	Low

Key: (+) = high; (-) = low.

Adapted from Centers for Disease Control. Management of persons exposed to multidrug-resistant tuberculosis. *MMWR* 1992;41(RR-11).

Low or intermediate likelihood of infection with MDRTB
If thought to be newly infected, these contacts should be evaluated for treatment of LTBI with isoniazid.

Intermediate, high intermediate, or high likelihood of infection with MDRTB
If thought to be newly infected, these contacts should be evaluated for an alternative treatment regimen according to their age and immune status:

- Contacts who are HIV-infected, otherwise immunosuppressed, and/or younger than 5 years of age should be given multidrug treatment with drugs other than isoniazid or rifampin. (See Table II-2 for regimens)

- Contacts who are HIV-negative, immunocompetent, and older than 5 years of age should be managed according to one of the following options:

TABLE II-2

Alternative Regimens for Treatment of Latent Tuberculosis Infection

	Medication	Daily Oral Dose (Maximum Dose)	Notes
ADULTS	**Option I** PZA and EMB	PZA: 15-20 mg/kg (2g) EMB: 15-25 mg/kg	The Centers for Disease Control and Prevention (CDC) recommend a 6-month course of treatment. However, the New York City Bureau of Tuberculosis Control recommends 6-12 months of treatment with this regimen because these drugs are bacteriostatic, not bacteriocidal.
	Option II PZA and a Fluoroquinolone	PZA: 15-20 mg/kg (2g) Levofloxacin: 500-1000 mg Ciprofloxacin: 750-1500 mg Ofloxacin: 600-800 mg	Treatment should last 6-12 months with this regimen.
	Option III Ethionamide and Cycloserine	Ethionamide: 15-20 mg/kg (1g) Cycloserine: 15-20 mg/kg (1g)	This regimen is recommended for contacts of a source patient whose isolate is resistant to PZA, EMB, and a fluoroquinolone. Treatment should last 12 months, and pyridoxine should be given with this regimen (see Section V).
CHILDREN	**Option IV** PZA and EMB	PZA: 15-20 mg/kg (2g) EMB: 15-25 mg/kg	This is the preferred regimen for children if the source patient's isolate is susceptible to these drugs and if the child's vision can be monitored. Treatment should last 12 months.
	Option V PZA and Ethionamide	PZA: 15-20 mg/kg (2g) Ethionamide: 15-20 mg/kg (1g)	This regimen may be used if the source patient's isolate is resistant to EMB or the child's vision cannot be monitored. Treatment should last 12 months.
	Option VI Ethionamide and Cycloserine	Ethionamide: 15-20 mg/kg (1g) Cycloserine: 15-20 mg/kg (1g)	This regimen may be used if the source patient's isolate is resistant to both PZA and EMB. Treatment should last 12 months, and pyridoxine should be given with this regimen (see Section V).

PZA = pyrazinamide EMB = ethambutol

Note: Quinolones are not approved by the Food and Drug Administration (FDA) for the treatment of children because of the potential for retarded skeletal growth. However, some pediatricians prescribe pyrazinamide and ciprofloxacin or ofloxacin in TST-positive children who are close contacts of an MDR-TB patient (see Option II above). The use of quinolones in children is being re-reviewed by the FDA and may be approved in the future.

Consider multidrug treatment for LTBI with anti-TB medications other than isoniazid or rifampin. (See Table II-2 for regimens.) This option is important for recent TST converters.

Do not administer any treatment. Educate the contact about the symptoms of TB. Evaluate the contact with a chest x-ray and symptom review at 3, 6, 9, 12, 18, and 24 months.

These options are summarized in Table II-3.

TABLE II-3

Options for Managing Contacts Who Are Likely to Be Infected with MDRTB*

Contact's Age and Immune Status	
Lmmunosuppressed or <5 Years Old	**Not Immunosuppressed and≥5 Years Old**
12 months of 2 drugs † (no INH or RIF)	12 months of 2 drugs, ‡ (no INH or RIF) or No treatment, and chest x-ray at 3, 6, 9, 12, 18, and 24 months

* "Likely to be infected" means an intermediate, high-intermediate, or high likelihood of infection with MDR-TB. See Table II-4.

† Isoniazid may be considered for the regimen, in addition to the two drugs, if the source patient's isolate is less than 100% resistant to isoniazid. Less than 100% resistance means that the isolate is resistant at low concentrations [0.2 μg/ml] but susceptible at high concentrations [1.0 μg/ml]. If isoniazid is added to the regimen, it should be given twice weekly at dosage of 900 mg.

‡ This is the suggested option for (1) recent TST converters, (2) persons with a high likelihood of infection with TB resistant to isoniazid and rifampin, and (3) children 10-14 years old who have an intermediate to high likelihood of infection with TB resistant to isoniazid and rifampin.

5. REGIMENS FOR WOMEN WHO BECOME PREGNANT WHILE TAKING TREATMENT OF LATENT TUBERCULOSIS INFECTION

In general, treatment of LTBI should be discontinued in women who become pregnant while taking isoniazid and/or rifampin for treatment of LTBI. To reduce the risk of peripartum hepatitis, treatment should not be restarted until 3 months after delivery. When treatment of LTBI is restarted, a full course should be given (previous doses ignored).

However, TST-positive pregnant women with certain risk factors should continue treatment for LTBI during the pregnancy:

- For women who are HIV-infected, who have behavioral risk factors for HIV-infection but decline HIV testing, or who have been in close contact with a smear-positive TB patient, treatment for LTBI should be continued, even during the first trimester.

- For women who have had a TST conversion within the past 2 years, treatment should be discontinued during the first trimester and resumed at the beginning of the second trimester. When treatment for LTBI is restarted, a full course should be given (previous doses ignored).

Pregnant women who are taking isoniazid should be prescribed pyridoxine (vitamin B6), 25 mg daily. Additional pyridoxine is not necessary for women who are already taking a prenatal vitamin that contains at least 25 mg of pyridoxine.

Breastfeeding should not be discouraged for an HIV-negative woman who is taking or planning to take any anti-TB medications. Breastfeeding infants whose mothers are taking isoniazid should receive supplemental pyridoxine.

6. REGIMENS FOR INDIVIDUALS WITH RADIOGRAPHIC EVIDENCE OF PRIOR, HEALED TUBERCULOSIS (CLASS IV)

TB Class IV comprises individuals who are unlikely to have TB disease at the time of the evaluation and who have the following:

- A TST reaction of greater than or equal to 5 mm

- A chest x-ray that shows non-calcified fibrotic lesions suggestive of prior, healed TB or silicosis

- A history of untreated or incompletely treated TB

- Three consecutive sputum tests collected on different days that have been submitted for AFB or smear-positive culture.

If bacteriologic results are negative, but activity or etiology of a radiographic abnormality is questionable, further evaluation with bronchoscopy or needle aspiration biopsy should be performed. In such situations, multidrug therapy can be started, and continued pending results of sputum culture. **Single drug treatment of LTBI should not be started until active TB has been excluded**.

Patients who begin multidrug therapy for suspected pulmonary TB Class V but are subsequently determined not to have active disease (i.e., AFB cultures are negative and chest radiographs are stable), should complete treatment with at least two months of a regimen containing rifampin and pyrazinamide if the tuberculin skin test is positive and other cases of the CXR abnormalities have been excluded.

Starting with a regimen of four drugs has several advantages over waiting to begin a single drug regimen after sputum cultures have returned negative: the risk of isoniazid resistance is significantly lower than with a regimen of isoniazid alone; adherence to treatment may be higher than with a 9-month regimen; and treatment can be initiated at the first medical visit rather than a later visit, after sputum cultures are shown to be negative for *M. tuberculosis*. In special circumstances, however, the physician may prefer to use a 9-month regimen.

The protocol for the four multidrug regimen is as follows:

- For all patients, perform baseline liver function tests and a complete blood count before starting the four-drug regimen.

- Collect three sputum specimens for acid-fast smears, cultures, and sensitivities.

- Start with a four-drug regimen of Rifamate (isoniazid and rifampin combined), pyrazinamide, and ethambutol administered by directly observed therapy (DOT). Prescribe pyridoxine if the patient is malnourished, alcoholic, HIV-infected, or pregnant.

- Ensure that treatment is monitored monthly by a physician.

- Continue all four drugs for 2 months, and obtain a repeat chest x-ray.

  If the chest x-ray shows no change, and the sputum cultures are negative for *M. tuberculosis,* the lesion presumably was inactive. Treatment may be discontinued if the patient has received a total of two months of treatment with a regimen containing rifampin and pyrazinamide (MMWR, Volume 49, RR-6, p.34). At the clinician's discretion, isoniazid and rifampin may be continued for an additional two months. If at four months of treatment, the chest x-ray remains stable and the sputum cultures are negative for *M. tuberculosis*, discontinue treatment.

  If the chest x-ray shows any resolution, the lesion presumably was active. Reclassify this patient as Class III, even if the cultures are negative. Continue isoniazid and rifampin for a total of six months of treatment in HIV-negative patients. Continue all four drugs for a total of six months of treatment in HIV-negative patients.

  If the four-drug regimen cannot be used because of adverse reactions or other reasons use isoniazid alone for a total of 9 months. Clearly document in the medical record the reason that a four-drug regimen could not be used.

II.D. Monitoring Patients During Treatment of Latent Tuberculosis Infection

Clinical monitoring is recommended for all patients who are undergoing treatment for latent TB infection, and is now emphasized over laboratory monitoring.

- Patients should be educated before treatment is initiated and at each follow up clinic visit about the possible side effects associated with their treatment, and advised to stop treatment and promptly contact their providers if side effects occur, or go to the emergency room if side effects are severe.

- Signs and symptoms include the following: unexplained anorexia, nausea, vomiting, dark urine, icterus, rash persistent parasthesias of the hands and feet, persistent fatigue, weakness or fever lasting 3 or more days, abdominal tenderness (especially right upper quadrant discomfort), easy bruising or bleeding, and arthralgia.

- Patients being treated for LTBI should receive follow up clinical evaluations at least monthly, when taking a single drug regimen of isoniazid or rifampin, and at 2, 4, and 8 weeks if taking rifampin and pyrazinamide. The evaluations should include careful questioning about side effects associated with their medication, particularly hepatitis, and a brief physical examination.

- Routine laboratory monitoring is indicated for patients whose baseline liver function tests were abnormal, and for patients at risk for hepatic disease. This includes pregnant women, or those in the immediate postpartum period (within 3 months of delivery), patients with HIV-infection, patients with a history of chronic liver disease (e.g., hepatitis B or C, patients with a history of alcoholic hepatitis, or cirrhosis), and patients who use alcohol regularly.

- Laboratory testing may also be indicated for evaluation of possible side effects to the medication, for example, liver function tests to evaluate patients with signs and symptoms of hepatotoxicity, or uric acid levels when patients complain of joint pain.

- Medication should be stopped if transaminase levels exceed 3 times the upper limit of normal if associated with symptoms and 5 times the upper limit of normal if the patient is asymptomatic.

II.E. Interrupted or Incomplete Treatment of Latent Tuberculosis Infection

Interrupted or incomplete treatment is defined as the loss of at least one third of the chosen treatment regimen, i.e., a lapse in treatment that lasted 2 or more consecutive months or intermittent interruptions in treatment that total 2 or more months.

Patients who are prescribed treatment of LTBI but do not complete the course of treatment should be encouraged to complete the treatment; recommendations for determining the duration of the new regimen are presented below. Do not restart if there has been more than one interruption in treatment.

1. PATIENTS WHO SHOULD START A NEW REGIMEN

In patients with one or more of the following conditions, the regimen should be completely renewed (i.e., the previous doses should be disregarded):

- A lapse in treatment within the first 3 months of the original regimen

- Treatment that lapsed more than 6 months ago

- Immunosuppression, especially due to HIV-infection

If treatment is restored after an interruption of more than two months, the TB history is updated and a new chest x-ray is obtained if there are symptoms of TB. Patients with an interruption in treatment for LTBI of six months or more should obtain a new chest x-ray before restarting treatment. The duration of the new regimen should correspond to the length of the original regimen (e.g., a new 9-month regimen in a patient originally prescribed 9-month regimen); a prolonged regimen is not necessary.

2. PATIENTS WHO SHOULD COMPLETE THE PREVIOUS REGIMEN

Patients with none of the conditions listed in II-E.(1) above, should continue and complete the originally prescribed treatment regimen. For example, if treatment lapsed for 2 months after completion of 3 months of a 6-month regimen, the patient should receive treatment for an additional 3 months for a total of 6 months treatment.

II.F. Completion of Treatment of Latent Tuberculosis Infection

Completion of therapy is based on the total number of doses administered, not on duration of therapy alone.

Isoniazid
Daily regimens
9 months: 270 doses, administered within a 12-month period
6-months: 180 doses, administered within a 9-month period

Isoniazid
Twice-weekly regimens (DOT only)
9-months: 76 doses, administered within a 12-month period
6-months: 52 doses, administered within a 9-month period

Rifampin (or Rifabutin) and Pyrazinamide (DOT only)
Daily regimen
2-months: 60 doses, administered within a 3-month period (DOT 5 days, self-administered 2 days)

Rifampin
Daily regimen
4-months 120 doses, administered within a 6-month period

A physician must decide the appropriate regimen for treatment of LTBI for an individual patient. Patients who self-administer their medication, and have demonstrated adherence to the regimen, may be discharged from clinic when they receive their final month's supply of medication (e.g., after the fifth month for patients taking a 6-month regimen for treatment of LTBI.

- The nurse or physician performing the monthly evaluation should document the completion of treatment and dismissal of the patient in the clinic medical record. The patient should receive documentation of his or her TB evaluation, the medication regimen, and the dates when treatment for latent TB infection was started and completed.

- The patient should be advised to return to clinic if he or she develops symptoms of tuberculosis, or side effects to the last month of self-administered medicine.

II.G. Follow-up for Patients Who Have Completed Treatment of Latent Tuberculosis Infection

Follow-up care, including chest x-rays and medical evaluations, is not necessary for patients who complete a course of treatment of LTBI, unless they develop symptoms of TB disease. However, a repeat course of treatment may be indicated for patients considered to be at high risk for progression to active disease in selected instances. For example, a repeat course of treatment for LTBI should be considered for HIV-infected individuals and children younger than 18 years who received treatment for LTBI in the past, but have subsequently been in close contact with a person who has infectious pulmonary or laryngeal TB disease. Exogenous re-infection is more likely if there are TST conversions among other contacts who had similar exposure to the infectious disease.

References

1. Centers for Disease Control. Control of tuberculosis in the United States. *Amer Rev Resp Dis* 1992; 146:1623-1633.

2. Centers for Disease Control. Treatment of tuberculosis and tuberculosis infection in adults and children. *Amer Rev Resp Dis* 1994; 149:1359-1374.

3. Centers for Disease Control and Prevention. Management of persons exposed to multidrug-resistant tuberculosis. *MMWR* 1992;41(RR-11).

III. Initial Evaluation for Tuberculosis Disease

Contents

The purpose of the evaluation is to

- Confirm current or old TB disease in Class V patients (individuals suspected of having TB disease)

- Assess all Class III patients (individuals confirmed to have TB disease) and Class V patients before they start treatment

Patients highly suspected of having current TB disease and expected to evolve as a Class III should be classified as Class V. For example, this classification would include a patient whose chest x-ray shows a cavitary lesion and infiltrates typical of active pulmonary TB. In contrast, patients suspected of having old, healed TB and expected to evolve as a Class IV should be classified as Class V — including, for example, a patient who has a positive tuberculin skin test reaction and has only nodules or linear shadows on the chest x-ray. All patients initially classified as Class V should be reclassified within 4 months of the initiation of anti-TB treatment, based on their culture and/or chest x-ray results (see Section VI-C).

III.A. Medical Evaluation and Physical Examination

Every individual classified as Class III or Class V must be given a medical evaluation, including a detailed history of the present illness, past history, a symptom review, a social history, and a physical examination as outlined in the form entitled “Medical Evaluation for Class III Patients" (see Appendix B). In addition, the protocol includes the following:

- If there is no documentation that a tuberculin skin test has been performed, it should be ordered, unless cultures for *M. tuberculosis* are positive. Anergy testing may be useful in some situations (see Section I-F[2]).

- All patients, including those without behavioral risk factors for HIV, should be counseled and offered HIV testing unless they have documentation of (1) a positive HIV antibody test or (2) a negative result to an HIV antibody test given less than 6 months ago. Patients younger than 18 years old or 65 and older should be counseled and offered testing if they have behavioral risk factors for HIV and have no documented history of a positive HIV test. Children >12 years may give consent for HIV testing if parental consent would be a deterrent.)

    - HIV-seronegative individuals who remain at risk for HIV infection during TB treatment should be retested within the first 5 months of treatment.

- If ethambutol is being considered for the regimen, a baseline visual acuity exam and Ishihara’s testing for color blindness will be performed.

- If an aminoglycoside or capreomycin is being considered for the regimen, a baseline audiogram should be performed.

- All patients should be asked about the following risk factors for MDR-TB: (1) previous, especially incomplete, treatment for TB; (2) close contact with a person who has MDR-TB; (3) previous hospitalization in a hospital with an outbreak of a drug-resistant strain of TB (especially if housed on the ward where the outbreak occurred); and (4) incarceration since 1990. If a patient has one or more of these risk factors, other anti-TB medication(s) should be considered in addition to isoniazid, rifampin, pyrazinamide, and ethambutol (see Section V). (Note: There is nothing unique about the initial clinical presentation of a patient with multidrug-resistant TB compared with a patient who has a susceptible strain.)

- All patients should be asked about their history of TB treatment. If the patient has previously received treatment, it is important to determine the drugs used, the duration of treatment, the history of adverse reactions, the reasons for discontinuation of treatment, and the previous drug susceptibility results.

- Female patients should be asked whether they may be pregnant. Women with menses more than 2 weeks late should be referred immediately for pregnancy testing. Pregnant women who are HIV seronegative or whose HIV status is unknown should be offered HIV counseling and testing, unless an HIV test has been done within the past 2 months. Pregnant women with TB disease should be managed according to the guidelines in Section IV-C.

- If the patient is a child, every effort should be made to identify the source patient's culture and susceptibility results, so the child's treatment regimen can be tailored appropriately. If the source patient has not been identified, a source case investigation should be performed (see Section VIII-E).

III.B. Chest X-Ray

A baseline chest x-ray should be obtained for all patients, except patients who can bring in a chest x-ray that has been performed within the past month and that can be filed in the Pulmonary Disease Services clinic. A written or oral report alone is not acceptable. Children younger than 5 years old (i.e., up to the date of the fifth birthday) should undergo both a posterior-anterior and a lateral chest x-ray. All other individuals should receive a posterior-anterior chest x-ray only; additional x-rays should be done at the physician's discretion.

Pregnant women who are being evaluated for active TB disease should undergo a chest x-ray without delay, even during the first trimester. A lead shield should be used for all chest x-rays in pregnant women.

Patients suspected of having extrapulmonary TB should also undergo a chest x-ray to rule out pulmonary TB. The diagnosis and treatment of extrapulmonary TB are discussed in Section IV-H.

III.C. Laboratory Tests

The following laboratory tests should be ordered for all patients:

- Reliable smears for acid-fast bacilli, cultures, and drug susceptibilities from sputum samples collected on 3 consecutive, separate days. Children who are unable to produce sputum spontaneously should have early morning gastric aspirates on 3 consecutive, separate days unless there is a known source with TB susceptabilities.

- Complete blood cell (CBC) count

- Chemistry panel (especially SGOT/AST, SGPT/ALT, alkaline phosphatase, total bilirubin, uric acid, blood urea nitrogen, and creatinine)

Currently, the only rapid diagnostic tests for TB that have been approved by the Food and Drug Administration are the Roche Polymerase Chain Reaction (PCR) Test (Amplicor®) and the Amplified *Mycobacterium tuberculosis* Direct (MTD) Test (Genprobe®). Both tests are approved only for smear-positive, previously untreated patients; the MTD test is approved only for respiratory specimens. A positive result to one of these tests should be confirmed by culture.

IV. Treatment of Tuberculosis Disease

Contents

IV.A. Regimen for HIV-Seronegative Patients

The following regimen is appropriate for HIV-seronegative, Class III or Class V adult patients with no risk factors for multidrug-resistant TB. Patients with behavioral risk factors for HIV infection who decline HIV testing should be treated with the regimen for HIV-seropositive patients.

- Start with a regimen of isoniazid, rifampin, ethambutol, and pyrazinamide for at least 2 months, unless there are absolute contraindications. Use Rifamate® or Rifater® (capsules combining isoniazid and rifampin) for patients who are not receiving directly observed therapy (DOT). See Table IV-1 for dosages.

- Discontinue ethambutol once the strain is known to be susceptible to isoniazid and rifampin. (It is not necessary to wait 2 months to discontinue ethambutol if the drug susceptibility results have come back sooner.) However, continue ethambutol if (1) drug susceptibility results show resistance to isoniazid or rifampin (see Section V), (2) drug susceptibility results are not available, *or* (3) thrice-weekly therapy was used from the beginning of treatment.

- Discontinue pyrazinamide after 2 months or when sputum smears become negative for acid-fast bacilli, whichever is later. However, continue pyrazinamide if (1) drug susceptibility results show resistance to isoniazid or rifampin (see Section V), (2) drug susceptibility results are not available, *or* (3) thrice-weekly therapy was used from the beginning of treatment.

- Maintain four drug therapy if compliance issues are problematic and patient may abscond from treatment.

Length of treatment:

- If the strain is fully susceptible, treat for a total of at least 6 months, or for at least 4 months beyond documented culture conversion, whichever is longer. (If the strain is drug resistant, see Section V for guidelines on the length of treatment.)

- If drug susceptibility results are not available, treat with four medications for at least 6 months, or for at least 4 months beyond documented culture conversion, whichever is longer.

- If the sputum cultures are negative but the patient has clinically diagnosed pulmonary TB, treat with four medications for at least 4 months.

- If smear positive at 60 days or if cultures have not converted by 4 months, assess the patient for adherence to treatment, absorption of anti-TB medication(s), and drug resistance. (See Sections V and VI.)

TABLE IV-1

Dosages for First-Line Anti-TB Medications

Medication	Daily Dose		Intermittent Dose (directly observed therapy only)		
			Twice-Weekly Dose		Trice-Weekly Dose
	Children	Adults	Children	Adults	
Isoniazid†*	10 mg/kg PO or IM Max 300 mg Adults less than 85 lbs. = 200 mg	300 mg PO or IM	20-40 mg/kg Max 900 mg	15 mg/kg Max 900 mg	15 mg/kg Max 900 mg
Rifampin†*	10-20 mg/kg PO or IV Max 600 mg Adults less than 90 lbs. = 450 mg	600 mg PO or IV	10-20 mg/kg Max 600 mg	600 mg	600 mg
Pyrazinamide*	20-30 mg/kg PO	1.5 g (<50 kg) 2.0 g (51-74 kg) 2.5 g (>75 kg) PO	40-50 mg/kg	2.5 g (<50 kg) 3.0 g (51-74 kg) 3.5 g (>75 kg)	2.0 g (<50 kg) 2.5 g (51-74 kg) 3.0 g (>75 kg)
Ethambutol	15-25 mg/kg PO	15-25 mg/kg PO Max 2.5 g	30-50 mg/kg	50 mg/kg	30 mg/kg
Streptomycin‡	20-40 mg/kg IM	15 mg/kg IM	25-30 mg/kg	25-30 mg/kg	25 mg/kg

† Isoniazid and rifampin are available as a combination capsule (Rifamate®) containing 150 mg of isoniazid and 300 mg of rifampin.
‡ In persons older than 60, the daily dose of streptomycin should be limited to 10 mg/kg.
* Isoniazid, Rifampin and Pyrazinamide are available as a combination capsule (Rifater®) containing 50 mg of Isoniazid, 120 mg and 300 mg of Pyrazinamide.

IV.B. Regimen for HIV-Seropositive and Other Immunosuppressed Patients

The following regimen is appropriate for Class III or Class V patients who have no risk factors for multidrug-resistant TB and who

- Are HIV seropositive, *or*
- Are otherwise immunosuppressed, *or*
- Have an unknown HIV status but have behavioral risk factors for HIV infection and decline HIV testing

1. STANDARD REGIMEN

- Start with a regimen of isoniazid, rifampin, ethambutol, and pyrazinamide for at least 2 months, unless there are absolute contraindications. Use Rifamate® and Rifater® (capsules combining isoniazid and rifampin) for patients who are not receiving DOT. See Table IV-1 for dosages.
- Discontinue ethambutol once the strain is known to be susceptible to isoniazid and rifampin. (It is not necessary to wait 2 months to discontinue ethambutol if the drug susceptibility results have come back sooner.) However, continue ethambutol if (1) drug susceptibility results show resistance to isoniazid or

rifampin (see Section V), (2) drug susceptibility results are not available, *or* (3) thrice-weekly therapy was used from the beginning of treatment.

- Discontinue pyrazinamide after 2 months or when sputum smears become negative for acid-fast bacilli, whichever is later. However, continue pyrazinamide if (1) drug susceptibility results show resistance to isoniazid or rifampin (see Section V), (2) drug susceptibility results are not available, *or* (3) thrice-weekly therapy was used from the beginning of treatment.

Length of treatment:

- If the strain is fully susceptible, treat for a total of at least 6 months, or for at least 4 months after documented culture conversion, whichever is longer. (If the strain is drug resistant, see Section V for guidelines on the length of treatment.)

- If drug susceptibility results are not available, treat with four medications for at least 6 months, or for at least 4 months beyond documented culture conversion, whichever is longer.

- If the sputum cultures are negative but the patient has clinically diagnosed pulmonary TB, treat with four medications for 6 months.

- If smear positive at 60 days or cultures have not converted by 4 months, assess the patient for adherence to treatment, absorption of anti-TB medication(s), and drug resistance. (See Sections V and VI.)

2. TB TREATMENT AND PROTEASE INHIBITORS

Protease inhibitors, a class of potent antiretroviral agents, are recommended for combination therapy with reverse transcriptase inhibitors in many HIV-infected patients.

These agents complicate TB treatment because they interact significantly with rifampin. Specifically, the concurrent use of protease inhibitors and rifampin significantly reduces the levels of protease inhibitors and significantly increases serum levels of rifampin. As a result, the protease inhibitors may lose their efficacy and the rifampin may have an increased toxic effect.

Rifampin is an important component of the standard TB treatment regimen. Regimens that include rifampin are shorter (6-9 months vs. 18-24 months) and have faster sputum conversion rates, higher cure rates, and lower relapse rates than regimens that do not include rifampin. HIV-infected TB patients who are treated without rifampin also have a higher risk of dying.

Short-term follow-up studies, however, have shown that rifabutin is probably equivalent to rifampin for treating TB.[1,2,3] The interaction of rifabutin with indinavir is the best studied and seems to be the least problematic. Saquinavir cannot be used with 300 mg/day of rifabutin because its already low levels are decreased by 40%; ritonavir raises rifabutin levels fourfold, increasing the risk of toxicity. Nelfinavir appears to interact with rifabutin similarly to indinavir, and this combination is another option. However, the indinavir-rifabutin interaction has been better studied.

Below are several suggested treatment regimens for patients for whom both protease inhibitors and anti-TB medications are indicated. (The Centers for Disease Control and Prevention [CDC] has also published recommendations,[4] which differ somewhat from those listed below.) Treatment recommendations vary according to whether the patient has already begun taking protease inhibitors when anti-TB treatment is initiated. To ensure the best outcome, patients must receive DOT for TB treatment, and providers of TB care and HIV care must coordinate their efforts.

Most patents who are not being treated with a protease inhibitor when they are diagnosed with TB should complete at least 2 months, and preferably 9 months, of a rifampin-containing regimen before starting

treatment with a protease inhibitor. When the regimen requires that patients complete some or all of their treatment for TB before starting protease inhibitor therapy, DOT is particularly important. By ensuring adherence, DOT minimizes the duration of treatment so that a protease inhibitor regimen can be initiated.

The decision about when to begin a protease inhibitor is based on the CD4+ T-lymphocyte count and other indications. For patients with low CD4+ counts (<200 cells/µl), the initiation of a protease inhibitor early during TB therapy may be indicated. A 9-month or a 12-month TB treatment regimen is recommended for these patients.

Once protease inhibitor therapy has been initiated and the patient has responded to therapy, most authorities recommend that the protease inhibitor be continued at the recommended dosages without interruption in order to prevent a rebound of HIV viremia or the development of resistance to protease inhibitors. Lower doses are associated with an increased risk for drug resistance, and there appears to be cross-resistance between currently available protease inhibitors.

Option 1. Delay treatment with a protease inhibitor until standard short-course (9-month) TB treatment is completed. In general, this option is appropriate for patients with a CD4+ T-lymphocyte count of ≥200 cells/µl.

Option 2. Start treatment with a protease inhibitor after the initial 2-month intensive phase of TB treatment with a rifampin-containing regimen. At this time, switch from rifampin to rifabutin 150 mg/day, and begin indinavir or nelfinavir (the usual recommended dose). Rifabutin can also be given twice or thrice weekly by DOT.[3] Use the same dosages of rifabutin and indinavir or nelfinavir whether TB therapy is daily or intermittent. With this option, TB treatment should last 9 months.

Option 3. Start treatment with a protease inhibitor after the initial 2-month intensive phase of TB treatment with rifampin-containing regimen. In the continuation phase of TB treatment, stop rifampin. Continue isoniazid, pyrazinamide, and ethambutol, and add any protease inhibitor. With this option, TB treatment should last 12 months.

Option 4. In patients already taking saquinavir or ritonavir when TB treatment is begun, (1) switch to indinavir or nelfinavir (the usual recommended dose) and (2) give rifabutin, 150 mg/day, as a substitute for rifampin in the TB regimen. This regimen is also appropriate for patients with a low CD4+ T-lymphocyte count or other indications for immediate therapy with protease inhibitors. After the initial 2-month intensive phase of TB treatment, patients receiving DOT may be given intermittent (twice or thrice weekly) therapy. With this option, TB treatment should last 9 months.

Option 5. If rifampin or rifabutin cannot be used for TB treatment, use an injectable anti-TB drug for the first 2 to 6 months of treatment, in combination with other anti-TB agents (isoniazid, pyrazinamide, and ethambutol). Any protease inhibitor can be used. TB treatment should last at least 18 months. The risk of patient mortality secondary to TB is likely to be higher with this alternative regimen than with a rifamycin-containing regimen.

3. TREATMENT OF COEXISTENT PULMONARY TB AND DISSEMINATED *MYCOBACTERIUM-AVIUM-INTRACELLULARE*

Severely immunosuppressed individuals can develop TB disease and disseminated *Mycobacterium avium-intracellulare* (MAI) infection concurrently, and must be treated for both conditions. Also, some AIDS patients with TB disease are candidates for preventive therapy against disseminated MAI infection. Clarithromycin and azithromycin are currently the first-line agents for preventing and treating MAI infection, but rifabutin has been used in the past.

Rifabutin should not be used at the same time as rifampin because of the added potential for toxicity. Whenever possible, another agent, such as clarithromycin or azithromycin, should be used instead of rifabutin. If another agent is used, rifampin can be continued in the anti-TB regimen. If another agent

cannot be used and rifabutin is required as preventive therapy for MAI, rifampin should be discontinued and rifabutin should be substituted for rifampin in the anti-TB regimen.

IV.C. Regimen for Pregnant Women

In almost all situations, a pregnant woman who has a positive *M. tuberculosis* culture (Class III) or who is suspected of having TB disease (Class V) should be treated without delay[1].

TB treatment regimens for pregnant women differ from standard treatment regimens because streptomycin is contraindicated and pyrazinamide should be avoided. Streptomycin has been shown to have teratogenic effects on the fetus, and pyrazinamide has an unknown effect on the fetus. However, if treatment is started after the first trimester, pyrazinamide should be included in the initial treatment regimen for HIV-seropositive women, women who have behavioral risk factors for HIV infection but decline HIV testing, and women suspected of having TB resistant to isoniazid and rifampin. Pyrazinamide should be included in the treatment regimen, regardless of the stage of pregnancy, for HIV-seropositive women strongly suspected of having TB resistant to isoniazid and rifampin. (Despite the lack of data on pyrazinamide, the World Health Organization recommends this drug at all stages of pregnancy, for all pregnant women.)

Whether a mother who has TB disease should be separated from her infant at delivery depends on the mother's infectiousness. Clinicians should assess the mother's infectiousness (see Sections VIII-A and VIII-C). If the mother is considered infectious, she should be separated from the infant until she becomes noninfectious or the infant starts preventive treatment.

1. STANDARD REGIMEN FOR HIV-SERONEGATIVE PREGNANT WOMEN

Following is the standard regimen for HIV-seronegative pregnant women with no risk factors for multidrug-resistant TB:

- Start with a regimen of isoniazid, rifampin, ethambutol, and PAS unless there are absolute contraindications. Use Rifamate® (capsules combining isoniazid and rifampin) for patients who are not receiving DOT. See Table IV-1 for dosages. (HIV-seronegative pregnant women who are suspected of having multidrug-resistant TB should be treated with the regimen described in Section IV-C[2].)

- Discontinue ethambutol and PAS once drug susceptibility results show full susceptibility to isoniazid and rifampin. (It is not necessary to wait 2 months to discontinue ethambutol if the drug susceptibility results have come back sooner.) However, continue ethambutol if (1) drug susceptibility results show resistance to isoniazid or rifampin (see Section V) or (2) drug susceptibility results are not available.

- For pregnant women taking isoniazid, give pyridoxine (25 mg a day), unless the patient is already taking a prenatal vitamin that contains the equivalent amount of pyridoxine.

Length of treatment:

- If the strain is fully susceptible, treat for a total of at least 9 months, or at least 6 months beyond documented culture conversion, whichever is longer. However, if pyrazinamide was given for the initial 2 months of treatment before the woman was discovered to be pregnant, a total of 6 months of treatment is appropriate. (If the strain is drug resistant, see Section V for guidelines on the length of treatment.)

[1] Very rarely treatment for TB disease may be deferred until the end of the first trimester if the pregnant woman meets all of the following criteria: Smear-negative for acid-fast bacilli; HIV-seronegative; No risk factors for HIV infection; No symptoms of TB (i.e., no cough, fever, nights sweats); No cavities on the chest x-ray(s)

- If drug susceptibility results are not available and pyrazinamide was not used during the initial 2 months of treatment, treat with isoniazid, rifampin, ethambutol, and PAS for at least 9 months, or for at least 6 months beyond documented culture conversion, whichever is longer.

- If the sputum cultures are negative but the patient has clinically diagnosed pulmonary TB, treat with isoniazid, rifampin, ethambutol, and PAS for 9 months.

- If smear positive at 60 days or if cultures have not converted by 4 months, assess the patient for adherence to treatment, absorption of anti-TB medication(s), and drug resistance. (See Sections V and VI.)

2. STANDARD REGIMEN FOR PREGNANT WOMEN WHO ARE IMMUNOSUPPRESSED OR SUSPECTED OF HAVING TB RESISTANT TO ISONIAZID AND RIFAMPIN

Following is the standard regimen for pregnant women who (1) are HIV seropositive or otherwise immunosuppressed, (2) have behavioral risk factors for HIV infection but decline HIV testing, or (3) are HIV seronegative but are strongly suspected of having multidrug-resistant TB (i.e., TB resistant to isoniazid and rifampin):

- If treatment is initiated *after* the first trimester, start with a regimen of isoniazid, rifampin, pyrazinamide, and ethambutol. Use Rifamate® (capsules combining isoniazid and rifampin) for patients not receiving DOT or Rifater® (capsules containing 50 mg of Isoniazid, 120 mg and 300 mg of Pyrazinamide.)

- If treatment is initiated *during* the first trimester, start with a regimen of isoniazid, rifampin, and ethambutol and PAS. (Use Rifamate® for patients not receiving DOT.) **However, use pyrazinamide only if the woman is HIV seropositive and, in addition, strongly suspected of having TB resistant to isoniazid and rifampin.**

- Discontinue ethambutol (and pyrazinamide, if used) once drug susceptibilities show full susceptibility to isoniazid and rifampin. (It is not necessary to wait 2 months to discontinue ethambutol if the drug susceptibility results have come back sooner.) However, continue ethambutol if (1) drug susceptibility results show resistance to isoniazid or rifampin (see Section V) *or* (2) drug susceptibility results are not available.

Length of treatment:

- If the strain is fully susceptible, treat for a total of at least 9 months, or for at least 6 months beyond documented culture conversion, whichever is longer. However, if pyrazinamide was given for the initial 2 months of treatment, a total of 6 months of treatment is appropriate. (If the strain is drug resistant, see Section V for guidelines on the length of treatment.)

- If drug susceptibility results are not available, treat with isoniazid, rifampin, and ethambutol for at least 9 months, or for at least 6 months beyond documented culture conversion, whichever is longer.
- If the sputum cultures are negative but the patient has clinically diagnosed pulmonary TB, treat with isoniazid, rifampin, and ethambutol for at least 12 months.

- If smear positive at 60 days or if cultures have not converted by 4 months, assess the patient for adherence to treatment, absorption of anti-TB medication(s), and drug resistance. (See Sections V and VI.)

3. ANTI-TB MEDICATIONS IN BREAST-FEEDING WOMEN

The small concentrations of anti-TB drugs in breast milk are not toxic to the nursing newborn. Therefore, breast-feeding should not be discouraged for an HIV-seronegative woman who is planning to take or is taking isoniazid or other anti-TB medications. Furthermore, the low concentration of anti-TB medications in breast milk should not be considered effective treatment for disease or as preventive treatment in a nursing infant. Women who are HIV seropositive should not breast-feed because of the risk of HIV transmission to the infant.

B_6 should be considered for infants breast-feeding with mothers on INH.

IV.D. Regimen for Children Who Cannot Be Evaluated for Visual Acuity or Color Vision

The following regimens are appropriate for children who cannot be evaluated for visual acuity or color vision. Those who can be assessed should be managed under the protocol for HIV-seronegative or HIV-seropositive adults, as appropriate.

Children who cannot be evaluated for visual acuity or color vision should not be treated with ethambutol unless the child is known or likely to have drug-resistant TB or HIV infection. In these situations, at the physician's discretion, ethambutol at a dosage of 15 mg/kg body weight may be included as part of the initial regimen.

Children with confirmed or suspected TB should be on DOT. If DOT is not given, the reason for this must be clearly documented in the medical record. After the intensive phase of daily therapy, children receiving DOT may be switched to an intermittent regimen. (See Section IV-G, Table IV-2, Methods 1 and 2.)

1. STANDARD REGIMEN FOR HIV-SERONEGATIVE CHILDREN WHOSE VISION CANNOT BE EVALUATED

Following is the standard regimen for HIV-seronegative children whose vision cannot be evaluated:

- Start with a regimen of isoniazid, rifampin, and pyrazinamide for at least 2 months, unless there are absolute contraindications. See Table IV-1 for dosages. For younger children, isoniazid or pyrazinamide tablets can be divided, crushed, or added to a small amount of food or liquids such as fruit, juice, or Jello. Also, rifampin may be emptied from the capsule and added to food or liquids.

- Use small amounts of fluid or liquids and ensure child completely ingests the mixture

- Discontinue pyrazinamide after 2 months. However, continue pyrazinamide if (1) drug susceptibility results for the child or the exclusive source patient show resistance to isoniazid or rifampin (see Section V) *or* (2) drug susceptibility results are not available. In children whose drug susceptibility results are not available, pyrazinamide may be discontinued after 2 months if the exclusive source patient is known to have TB susceptible to isoniazid and rifampin.

- If the exclusive source patient is known or strongly suspected to have pulmonary or laryngeal TB resistant to isoniazid and/or rifampin, use ethambutol if necessary, along with other appropriate medications. See Section V.

Length of treatment:

- If the strain is fully susceptible, treat for at least 6 months, or for at least 4 months beyond documented culture conversion, whichever is longer. (If the strain is drug resistant, see Section V for guidelines on the length of treatment.)

- If drug susceptibility results are not available, treat with isoniazid, rifampin, and pyrazinamide for at least 6 months, or for at least 4 months beyond documented culture conversion, whichever is longer.

- If the sputum cultures are negative but the child has clinically diagnosed pulmonary TB, treat with isoniazid, rifampin, and pyrazinamide for 6 months.

- If cultures have not converted by 3 months, assess the child for adherence to treatment, absorption of anti-TB medication(s), and drug resistance. (See Sections V and VI.)

2. STANDARD REGIMEN FOR HIV-SEROPOSITIVE AND OTHER IMMUNOSUPPRESSED CHILDREN (IF VISION CANNOT BE EVALUATED)

Following is the standard regimen for children who are HIV seropositive or otherwise immunosuppressed, as well as children with risk factors for HIV infection whose parent(s) or guardian(s) declines HIV testing:

- Start with a regimen of isoniazid, rifampin, pyrazinamide, and ethambutol at 15 mg/kg. However, if the exclusive source patient is known to have TB susceptible to isoniazid and rifampin, ethambutol may be omitted from the initial regimen.

- Discontinue ethambutol once the strain is known to be susceptible to isoniazid and rifampin. (It is not necessary to wait 2 months to discontinue ethambutol if the drug susceptibility results have come back sooner.) However, continue ethambutol if (1) drug susceptibility results show resistance to isoniazid or rifampin (see Section V) *or* (2) drug susceptibility results are not available.

- Discontinue pyrazinamide after 2 months. However, continue pyrazinamide if (1) drug susceptibility results show resistance to isoniazid or rifampin (see Section V) *or* (2) drug susceptibility results are not available (unless the exclusive source patient is known to have TB susceptible to isoniazid and rifampin).

Length of treatment:

- If the strain is fully susceptible, treat for a total of at least 6 months, or for at least 4 months beyond documented culture conversion, whichever is longer. (If the strain is drug resistant, see Section V for guidelines on the length of treatment.)

- If drug susceptibility results are not available for the child or the exclusive source patient, treat with four medications for at least 6 months, or for at least 4 months beyond documented culture conversion, whichever is longer.

- If the sputum cultures are negative but the child has clinically diagnosed pulmonary TB, treat with four medications for 6 months. (However, if the exclusive source patient is known to have TB susceptible to isoniazid and rifampin, treat with isoniazid, rifampin, and pyrazinamide for 2 months, followed by isoniazid and rifampin for 4 months.)

- If cultures have not converted by 3 months, assess the child for adherence to treatment, absorption of anti-TB medication(s), and drug resistance. (See Sections V and VI.)

IV.E. Regimen for Patients with Chronic Renal Failure

In most patients with chronic renal failure, the regimens for TB treatment must be adjusted. Most experts advise lengthening the interval between conventional doses as the safest method to accomplish adequate

but safe serum levels. The following anti-TB medications are eliminated by the kidney and therefore require a regimen adjustment:

AMINOGLYCOSIDES AND CAPREOMYCIN
These medications can be used in conventional or 750-mg doses, but only twice or thrice weekly. The dose should be administered 6 to 8 hours before dialysis in patients who are receiving maintenance hemodialysis.

PYRAZINAMIDE
In patients with mild to moderate renal insufficiency, pyrazinamide can be used at the usual daily dose. In patients with severe renal failure, however, twice- or thrice-weekly doses of 40 mg/kg are recommended. The medication should be given 24 hours before dialysis.

PARA-AMINOSALICYLIC ACID
Traditional formulations of para-aminosalicylic acid (PAS) may worsen renal acidosis and provide an excessive sodium load; these should be avoided. However, formulations of PAS that do not use the sodium salt (i.e., Paser®) can be used without the hazard of sodium retention.

ETHAMBUTOL AND CYCLOSERINE
These medications are excreted primarily by the kidney, and excessive and toxic blood levels can occur in patients with chronic renal insufficiency. Both medications should be avoided if possible. If ethambutol is essential to the regimen in patients with multidrug-resistant TB, a conventional 15 mg/kg dose may be given every 2 or 3 days, but visual acuity and color vision must be very closely monitored and blood levels must be monitored. Doses should be given 4 to 6 hours before dialysis.

QUINOLONES
Ciprofloxacin has less renal excretion than sparfloxacin, levofloxacin, or ofloxacin and is preferred in cases of chronic renal failure. A reduction of the dose to 500 mg, once daily, is suggested for patients on hemodialysis or peritoneal dialysis.

Isoniazid, rifampin, and ethionamide can be used in conventional doses in patients with chronic renal failure.

IV.F. Directly Observed Therapy (DOT)

The standard of care in TB treatment, DOT is the best way to ensure that patients complete an adequate course of TB treatment. DOT means that a health care worker or another responsible individual directly observes and supervises every dose of anti-TB medication taken by the patient. DOT regimens may be daily, twice weekly, or thrice weekly; once-a-week DOT is not acceptable.

Most patients will adhere to treatment when education, incentives, housing, enhanced social services, and home or field DOT is provided. If these less restrictive measures are likely to fail, or have already failed, California State Health and Safety code empowers the Health Officer to issue patients any order deemed necessary to protect the public health (e.g., orders for isolation, or long-term detention).

1. PROTOCOL FOR PROVIDING DOT

All TB Class III and Class V patients should be given DOT. DOT is mandatory for patients at high risk, including patients with MDR disease, immunosuppression, and previous noncompliance. When a patient is not started on DOT, the compelling reason(s) must be clearly documented in the medical record.

Patients being cared for by a non health department physician may also receive DOT by Orange County Health Care Agency Pulmonary Disease Services. In this situation, the Physician-in-Charge in Pulmonary Disease Services must review the patient's medical regimen and treatment plan at least monthly.

IV.G. Intermittent Regimen

For patients with drug-susceptible TB, intermittent therapy (i.e., regimens given twice or thrice weekly) is well documented to be at least as effective as a daily regimen. Intermittent therapy is easier to supervise than daily therapy, and it helps ensure adherence. The methods of intermittent treatment are described in Table IV-2.

Intermittent therapy should be given only under a DOT program.

Patients with resistance to rifampin alone or to both isoniazid and rifampin should not be treated with an intermittent treatment regimen.

If non-adherence to twice- or thrice-weekly DOT occurs, daily DOT should be instituted.

TABLE IV-2

Methods of Intermittent Treatment

	Weeks of Treatment								
Method	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9 and longer (to end of treatment)**
1*	Daily								Intermittent (2x or 3x weekly) with DOT
2	Daily		Intermittent (2x weekly) with DOT						

***** This is the preferred initial regimen for an individual who has fairly advanced disease or risk factors for MDR-TB. If MDR-TB is confirmed, follow the guidelines in Section V.

For methods 1 and 2:

- Discontinue ethambutol once the strain is known to be susceptible to isoniazid, rifampin, and pyrazinamide.
- Discontinue pyrazinamide after 2 months, or when sputum smears become negative for acid-fast bacilli, whichever is later. However, continue pyrazinamide if (1) drug susceptibility results show resistance to isoniazid or rifampin (see Section V) or (2) drug susceptibility results are not available.
- If susceptibility results are not available, continue all four medications daily, twice, or thrice weekly for the duration of treatment.

IV.H. Evaluation and Treatment of Extrapulmonary TB

The basic principles that underlie the treatment of pulmonary TB also apply to extrapulmonary forms of the disease. As a general rule, regimens that are adequate for treating pulmonary TB in adults and children are also effective for treating extrapulmonary disease, because in most cases the mycobacterial burden is considerably smaller in the latter. However, for certain forms of extrapulmonary disease, such as central nervous system, bone, and joint TB, the continuation phase of treatment may be prolonged.

Following is a discussion of special issues in managing certain extrapulmonary forms of TB. The issues presented are those usually faced in the diagnosis of TB and the treatment of the patient in the acute, hospitalization phase, before the patient arrives in Pulmonary Disease Services for follow-up care. Therefore, many of these procedures and decisions may not be made by physicians in Pulmonary Disease Services.

This section also presents suggested treatment regimens for various extrapulmonary forms of TB and lists the follow-up specimens that should be obtained. However, only general guidelines are presented here; for more details on the management of extrapulmonary TB, see Des Prez RM and Haas DW. *Mycobacterium tuberculosis*. In: Mandell GL, Bennett JE, Dolin R. *Principles and Practice of Infectious Diseases, Fourth Edition*. NY.- Churchill Livingston; 1995.

1. TUBERCULOUS MENINGITIS

DIAGNOSIS

The key diagnostic procedure is the examination of the cerebral spinal fluid (CSF). The characteristic findings of the CSF are pleocytosis (65% of cases have white blood cell counts between 100-500) with lymphocytic predominance (seen in 73% of the cases in one series); elevated protein and low glucose are usual. Acid-fast bacilli have been seen in up to 37% of cases on initial examination, and in up to 87% of cases when the fluid from four serial spinal taps has been examined. Nucleic acid amplification techniques may assist in the diagnosis of tuberculous meningitis and other extrapulmonary forms of disease, but a negative nucleic acid test does not rule out TB disease.

TREATMENT

Isoniazid, rifampin, and pyrazinamide penetrate the blood-brain barrier sufficiently; ethambutol, the aminoglycosides, and capreomycin penetrate only when meninges are inflamed. Flouroquinlones should also be used. For information on the penetration of anti-TB medications in the central nervous system, see Appendix D. When multidrug-resistant TB is unlikely, tuberculous meningitis can be treated with isoniazid, rifampin, pyrazinamide, and ethambutol, in doses comparable to those used for pulmonary TB, for the first 2 months. This phase should be followed by a regimen of isoniazid, rifampin, and pyrazinamide for 7-10 additional months in immunocompetent individuals and at least 10 additional months in children and immunosuppressed individuals.

USE OF CORTICOSTEROIDS

Many authorities advocate the use of corticosteroids in patients who are initially confused, stuporous, or have focal neurologic deficits, dense paraplegia or hemiplegia, or "CSF block." Also, some authorities consider evidence of cerebral edema on a CT scan to be an indication for corticosteroid therapy.

Prednisone should be started at a dosage of 60-80 mg daily. The dose should be gradually reduced after 1 or 2 weeks, with the patient's symptoms as a guide. If the patient has responded to treatment, steroids can, in most cases, be discontinued entirely after 4 to 6 weeks.

2. DISSEMINATED TB

Disseminated TB is a result of the hematogenous spread of *M. tuberculosis* from primary infection or organs with chronic foci of TB.

DIAGNOSIS

Disseminated TB is usually suspected because of the presence of miliary infiltrates on a chest x-ray. Transbronchial biopsy is the highest-yielding procedure for obtaining tissue. In other instances, there is evidence of hematogenous dissemination from a tissue biopsy of other organs, such as the lymph nodes, liver, or bone marrow.

In many AIDS patients with hematogenous dissemination, urine or blood cultures obtained by appropriate techniques yield *M. tuberculosis*. These patients should be assumed to have miliary TB, even in the absence of radiologically or pathologically demonstrated TB lesions in other organs.

TREATMENT

Disseminated TB should be treated according to the regimen for tuberculous meningitis.

USE OF CORTICOSTEROIDS

Fulminant miliary TB may be associated with the adult respiratory distress syndrome (ARDS) and disseminated intravascular coagulation (DIC). In such cases, corticosteroid treatment (prednisone 60-80 mg/day) is indicated. Many authorities also advise the use of corticosteroids in severely ill persons with a delayed initial response to chemotherapy, if drug resistance has been ruled out.

3. TUBERCULOUS LYMPHADENITIS

Tuberculous lymphadenitis most commonly affects cervical or supraclavicular lymph nodes.

DIAGNOSIS
The diagnosis can be established by the culture of *M. tuberculosis* from lymph node biopsy or aspirate. Demonstration of acid-fast bacilli in tissue (seen in slightly over half of cases) or aspirate or pathologic evidence of caseating granuloma is consistent with TB or nontuberculous mycobacterial infection. Aspiration is also useful especially if the node(s) demonstrate fluctuance. Individuals suspected of having tuberculous lymphadenitis should be referred for biopsy or aspiration.

TREATMENT
Tuberculous lymphadenitis should be treated according to the regimens for pulmonary TB. Even if lymph node excision is complete, chemotherapy is indicated. The patient's clinical response should be carefully considered in determining the length of treatment; decisions about the duration of treatment should be individualized.

4. SKELETAL TB

Skeletal TB (TB of the bones and joints) usually occurs in the weight-bearing joints. TB in the spine (Pott's disease) is the most common, followed by TB in the hip and knee. The typical presenting symptoms are pain and difficulty with locomotion.

DIAGNOSIS
Skeletal TB is diagnosed by x-ray films of the involved joint, followed by specimen collection and culture. A tissue biopsy is necessary to confirm the diagnosis and perform susceptibility testing. All individuals suspected of having bone or joint TB should be referred for an appropriate biopsy or aspiration.

TREATMENT
Skeletal TB should be treated according to the regimen for TB meningitis, although some authorities advise 12 months of treatment for all individuals, regardless of immune status. Most patients with skeletal TB who are treated in Orange County Health Care Agency Pulmonary Disease Services should also be followed by an orthopedist.

5. RENAL TB

DIAGNOSIS
Approximately 90% of patients with renal TB have abnormal urinalysis results (usually gross or microscopic hematuria and/or pyuria). Also, in 90% of patients, the culture of three morning urine specimens shows *M. tuberculosis*.

TREATMENT
In general, regimens for treating pulmonary TB are highly successful for treating renal TB. Surgery is indicated only for intractable pain, persistent nontuberculous infection from obstruction, or serious, persistent hematuria. Treatment is the same as pulmonary tuberculosis. All patients with renal TB who are treated in Pulmonary Disease Services should also be followed by a urologist.

6. GASTROINTESTINAL TB

TB can affect any part of the gastrointestinal tract, from the tongue or oropharynx to the anus. The cecum is the most common gastrointestinal site. Evidence of coexistent pulmonary TB is present in only 25% to 50% of cases. The most common symptoms are anorexia, early satiety, abdominal pain, or symptoms of intestinal obstruction.

DIAGNOSIS
Many patients with gastrointestinal TB have a stool culture that is positive for *M. tuberculosis*. It must be decided whether the positive culture represents organisms from a gastrointestinal, source or organisms that were swallowed from the pulmonary source.

In individuals with confirmed pulmonary TB and no evidence of intestinal obstruction, further evaluation to seek the gastrointestinal source is usually unnecessary, because the treatment is identical for pulmonary and gastrointestinal TB.

If there is no evidence of pulmonary TB, ulcerative lesions can be discerned by an upper gastrointestinal series with small-bowel follow through. If no lesions are found in the upper gastrointestinal tract, the lower gastrointestinal tract can be evaluated by air-contrast barium enema, Alternatively, endoscopy and/or colonoscopy can be used to visualize the lumen and obtain specimens for acid-fast bacilli and other cultures.

The demonstration of acid-fast bacilli in stool specimens has no diagnostic significance, because water and certain foods are often contaminated by environmental saprophytic mycobacteria that transverse the gastrointestinal tract and are excreted.

Carbofuscin, the standard stain for cyclospora in stool specimen, is also a basic stain for mycobacteria. Reports of stool specimens examined for cyclospora and positive for acid-fast bacilli should be assumed to be saprophytes unless a stool culture yields *M. tuberculosis.*

TREATMENT
Gastrointestinal TB should be treated according to a regimen for pulmonary TB. A gastroenterologist should also follow patients with gastrointestinal TB treated in Pulmonary Disease Services.

7. PERICARDIAL TB

Pericardial TB is much more common in HIV-infected individuals. The onset may be subtle (dominated by cardiovascular consequences of effusion) or abrupt (fever and precordial pain).

DIAGNOSIS
Fluid from pericardiocentesis is similar to fluid from tuberculous pleural effusion. Positive smears for acid-fast bacilli are not common, and cultures are positive in only 25% to 50% of cases. Some authorities do not advocate pericardiocentesis as part of the diagnostic work-up because of the risks of the procedure and the limited benefit in terms of immediate treatment. Some physicians advocate primary surgical intervention with a pericardial "window" and biopsy in every case of suspected TB pericarditis. Other authorities recommend pericardiocentesis or surgical biopsy to obtain culture and susceptibility information, unless there is a positive culture from another source.

TREATMENT
Pericardial TB should be treated according to a regimen for pulmonary TB.

USE OF CORTICOSTEROIDS
Corticosteroids are generally recommended. If used, begin prednisone at 60-80 mg daily, and gradually decrease the dosage over a period of several weeks as the effusion subsides.

USE OF PERICARDIECTOMY
Pericardiectomy is indicated if there is chronic constriction with hemodynamic consequences.

8. PLEURAL TB

DIAGNOSIS
In pleurocentesis, acid-fast bacilli stains of the fluid sediment are seldom positive; cultures are positive in 25% to 33% of cases. A transthoracic needle pleural biopsy is used routinely to establish or support a diagnosis of TB pleuritis, based on the demonstration of caseating granuloma with or without acid-fast bacilli on tissue stains. In nearly 100% of cases, a small open pleural biopsy is diagnostic of pleural TB. Although a chest x-ray may show no visible parenchymal lesions, cultures of sputum or gastric fluid are positive in 25% to 33% of cases.

TREATMENT
Pleural TB should be treated according to a regimen for pulmonary TB.

9. TUBERCULOUS PERITONITIS

DIAGNOSIS
Tuberculous peritonitis may or may not be associated with systemic symptoms, such as fever, night sweats, fatigue, weight loss, etc. Usually, the disease presents with 1 of 2 manifestations: (1) the presence of ascites that lead to abdominal pain and distention, with or without gastrointestinal symptoms; or (2) abdominal pain, with or without symptoms suggesting intestinal obstruction. The diagnosis of tuberculous ascites is made usually by culture of the ascitic fluid or peritoneal or open biopsy; the diagnosis of "dry" tuberculous peritonitis is usually made by laparotomy and biopsy that reveals caseating granulomas, with or without tissue stains positive for acid-fast bacilli.

TREATMENT
Tuberculous peritonitis should be treated with a regimen for pulmonary TB. Any individual suspected of having tuberculous peritonitis should be referred to an appropriate gastrointestinal clinic or hospital for diagnostic investigation. If possible, treatment should not be initiated without a diagnostic evaluation.

IV.I. Use of Pyridoxine (Vitamin B_6) in TB Treatment

Pyridoxine is often used in conjunction with certain anti-TB medications to prevent side effects in the central and peripheral nervous system (see Table IV-3).

TABLE IV-3

The Use of Pyridoxine in TB Treatment

Drug	Dosage of Pyridoxine	Indications
Isoniazid (INH)	25 mg for each 300 mg of INH or 50 mg twice weekly, if INH given at 900 mg twice weekly	Indicated for children on a meat- and milk-deficient diet and for breast-feeding infants. Also consider for patients with HIV infection Malnourishment (≥10% below ideal body weight or any wasting disease Diabetes Cancer Chronic renal disease Pregnancy Chronic liver disease Alcoholism Pre-existing peripheral neuropathy
Ethionamide (ETH)	25 mg with each dose of ETH, regardless of ETH dose	Same indications as INH.
Cycloserine	50 mg for each 250 mg of cycloserine, to a maximum of 200 mg pyridoxine daily*	Required for all patients taking cycloserine.

*` If an individual is taking 500 mg of cycloserine at the first dose and 250 mg at the second dose, for simplicity, 100 mg of pyridoxine

IV.J. Interrupted or Incomplete Treatment

Interrupted or incomplete treatment is defined as the loss of at least one third of the intended anti-TB regimen—in other words, a lapse in treatment that lasted 2 or more consecutive months or intermittent interruptions in treatment that total 2 or more months.

1. GENERAL PRINICIPLES

When a patient has had interrupted or incomplete treatment, the physician must decide the appropriate duration of a new regimen. This decision should be based on an estimate of the load of viable tubercle bacilli remaining in the lungs when treatment is restarted.

Certain factors suggest a large mycobacterial load:

SHORT PERIOD OF TREATMENT BEFORE THE LAPSE
Continuous treatment is more crucial at the beginning of the regimen (i.e., during the first 3 months) because of the need to decrease the bacterial load. Toward the end of anti-TB treatment, there are fewer persisting organisms to kill. Therefore, patients who had a lapse in treatment early in the course of the regimen are more likely to have a large mycobacterial residual and may require a complete renewal of the anti-TB regimen.

PROLONGED LAPSE IN TREATMENT
The longer the lapse in treatment, the more likely a patient is to have a large mycobacterial load.

PROLONGED PERIOD OF TREATMENT REQUIRED IN INITIAL REGIMEN BEFORE CULTURES CONVERTED TO NEGATIVE
Patients who required prolonged treatment before culture conversion to negative or who did not have culture conversion to negative are more likely to have a large mycobacterial load and may require a complete renewal of the regimen.

In contrast, patients whose cultures converted to negative promptly before the lapse in treatment and whose cultures are still negative when treatment is restarted may not require a complete renewal of the regimen. Instead, the new regimen should last as long as needed to complete the duration of the regimen originally prescribed. For example, consider a patient who was originally prescribed 6 months of treatment. If this patient had received 3 months of uninterrupted treatment and had negative cultures before and after a lapse in treatment, the new regimen should last 3 months, so as to complete a total of 6 months of treatment.

EXTENSIVE DISEASE INITIALLY, ESPECIALLY CAVITARY
Patients with extensive disease are more likely to have a large mycobacterial load and may require a complete renewal of the regimen.

2. PROTOCOL FOR RESTARTING TREATMENT

- In patients with one or more of the following conditions, treatment should be completely renewed (i.e., the previous doses should be disregarded):

  a. A lapse in treatment within the first 3 months of the original regimen

  b. Treatment that lapsed more than 6 months ago

  c. Extensive disease, especially cavitary

  d. Immunosuppression, especially due to HIV infection

  e. Prolonged treatment before culture conversion to negative or no culture conversion to negative

The duration of the new regimen should be based on current clinical indications; a prolonged regimen is not necessary.

- In patients with none of the conditions listed in (a)-(e) above, the regimen should last as long as needed to complete the duration of the regimen originally prescribed. For example, if treatment lapsed for 2 months after 3 months of an intended 6-month regimen, the patient should receive treatment for an additional 3 months so as to complete a total of 6 months of treatment. Caveat: the patient must receive four months of treatment after culture conversion.

- When treatment is reinstituted, sputum samples should be taken for smear and culture. In addition, drug susceptibility testing should be repeated at this time, even if the pretreatment isolates were pansusceptible.

- DOT should be instituted if the patient is not currently receiving DOT. Every attempt should be made to ensure that the patient completes a continuous course of anti-TB treatment.

- If a patient fails to adhere to DOT, an Individualized Health Officer's Order for DOT should be requested.

IV.K. Treatment Failure

Treatment failure is defined as a positive *M. tuberculosis* culture any time after 4 months of appropriate anti-TB treatment in a patient with pansusceptible TB. Treatment failure should be suspected in patients whose cultures are pending and who have clinical deterioration due to TB or worsening of the chest x-ray due to TB. It is our practice to evaluate persistently smear-positive and culture-positive patients at 60 days. This evaluation includes a review of drug susceptibility testing, drug level studies, as well as other predisposing factors for treatment failure.

- This evaluation includes a review of the most recent positive *M. tuberculosis* culture, if one is available, should be tested for susceptibility to first- and second-line drugs. If strongly smear-positive for acid-fast bacilli, direct susceptibility testing should be requested from the Orange County Health Care Agency Pulmonary Disease Services.

- Contact Orange County Health Care Agency Public Health for drug level studies.

Patients who are clinically stable may be maintained on the current anti-TB regimen ("holding regimen") until susceptibility results are available to guide the choice of medications.

A single anti-TB medication should never be added to a regimen that is failing (i.e., if the patient is not clinically improving or if the cultures are still positive 4 months after the initiation of therapy.) At least two, and preferably three, new anti-TB medications to which the strain is likely to be susceptible should be added.

DOT should be instituted if the patient is not currently receiving DOT.

If a patient fails to adhere to DOT, an Individualized Health Officer's Order for DOT should be requested.

IV.L. Surgery for Pulmonary TB

Surgery is not a first-line option in the treatment of TB because in most cases, pulmonary TB is curable using modern drug regimens. Surgery is, however, one of the last alternatives available for individuals with certain multidrug-resistant TB strains, in whom chemotherapy has failed or is not possible because of a lack of sufficient and effective medications.

1. INDICATIONS FOR SURGERY

In joint consultation with medical and surgical experts, surgery can and should be considered an adjunct to chemotherapy when all of the following criteria are met:

- Adequate first- and second-line regimens of anti-TB medications have failed to cure or cause *M. tuberculosis* cultures to convert to negative within 4 to 6 months.

- The disease is sufficiently localized to allow lobectomy or pneumonectomy.

- The remaining lung tissue is relatively free of disease.

- The patient has an acceptable surgical risk, with sufficient pulmonary reserve to tolerate the resection.

Other clinical circumstances, such as major bronchial obstruction, severe hemoptysis, or bronchopleural fistula (BPF) are other possible indications for surgery.

2. PROTOCOL FOR SURGERY REFERRAL

Referrals for surgery should be made on an individual basis, and should be reviewed and coordinated by the Medical Director and TB Controller.

Clinic physicians may refer a patient for a CT scan when necessary, after consulting with the Medical Director.

- As part of the medical/surgical evaluation, all of the following should be documented:
  - + Failure to cure TB, as evidenced by persistent positive *M. tuberculosis* sputum cultures, or reversion from negative to positive cultures, despite the best treatment regimen possible and every effort to achieve adherence to treatment, including the use of DOT
  - + Diagnostic evaluation that reveals that the majority of disease is anatomically localized to allow surgical resection
  - + Appropriate evaluation that reveals that the patient has an acceptable surgical risk
- Even after lung resection, the patient must complete a full course of treatment with medications to which the *M. tuberculosis* strain is susceptible.
- Referrals should be made on the referral form to Chest Surgery, University of California, Irvine. Clinic physicians are encouraged to present these cases in advance, if clinically possible, at the combined monthly conference at UCI.

References

1. Gonzalez-Monataner LJ, et al. Rifabutin for the treatment of newly diagnosed pulmonary tuberculosis: a multinational, randomized, comparative study versus rifampicin. *Tubercle and Lung Disease* 1994;75:341-347.

2. Schwander S, et al. A pilot study of antiberculosis combinations comparing rifabutin with rifampicin in the treatment of HIV-1 associated tuberculosis. *Tubercle and Lung Disease* 1995; 75:210-218.

3. McGregor MM, Olliaro P, Wolmarans L, et al. Efficacy and safety of rifabutin in the treatment of patients with newly diagnosed pulmonary tuberculosis. *Am J Respir Crit Care Med* 1996;154:1462-1467.

4. Centers for Disease Control and Prevention. Clinical Update: Impact of HIV protease inhibitors on the treatment of HIV-infected tuberculosis patients with rifampin. *MMWR* 1996;45:921-925.

V. Treatment of Drug-Resistant Tuberculosis

Contents

V.A. Principles of Treating Drug-Resistant TB

Unlike the treatment of drug-susceptible TB, it is not possible to develop standardized protocols for the treatment of known or suspected drug-resistant TB. Several issues are involved: first, any treatment recommendation must take into account the drug susceptibility results of the individual isolate; second, good data are lacking on the efficacy of non-standard regimens; and third, side effects to second-line medications, often serious and intolerable, may preclude the use of these drugs for the recommended period of time.

In this protocol, multidrug-resistant TB (MDR-TB) refers to a strain of *M. tuberculosis* resistant to at least isoniazid and rifampin.

1. MDR-TB should never be treated without expert consultation. The treatment of MDR-TB can be as complex as cancer chemotherapy and should not be attempted without the consultation of a specialist in MDR-TB treatment.

2. Patients must be treated with a regimen of at least two, and preferably three, anti-TB medications to which the strain is likely to be susceptible.

3. A single anti-TB medication should never be added to a regimen that is failing (i.e., if the patient is not clinically improving or if the cultures are still positive 4 months after the initiation of therapy.) At least two, and preferably three, new anti-TB medications to which the strain is likely to be susceptible should be added.

4. Treatment for TB strains resistant to at least isoniazid and rifampin should be given for at least 18 months after culture conversion to negative, and for up to 24 months after culture conversion to negative in some HIV-seropositive individuals or those with cavitary disease.

5. Patients with MDR-TB must be treated under a program of directly observed therapy (DOT.

6. Patients with MDR-TB should not be treated with intermittent therapy regimens.

7. If a patient has a positive *M. tuberculosis* culture after 4 months of treatment, the most recent positive culture must be sent to the clinical laboratory for first- and second-line anti-TB drug susceptibility testing. If the individual has a 2+, 3+, or 4+ positive smear for acid-fast bacilli, direct susceptibility testing of the sputum sample should be ordered. It is not necessary to wait for growth of the specimen before susceptibility testing is done. While the drug susceptibility results are pending, at least two treatment alternatives are available:

   - If the patient is not acutely ill or clinically deteriorating, the current or most recent anti-TB regimen may be continued until the new drug susceptibility results are available. This regimen is often referred to as a “holding regimen.”

   - If the patient is acutely ill or clinically deteriorating, at least two new medications should be started, based on an assessment of the remaining medications to which the strain is likely to be susceptible. In addition, the original medications should be continued until the new drug susceptibility results are available.

8. If a regimen is not failing (i.e., the patient has shown clinical improvement and *M. tuberculosis* cultures have converted from positive to negative), but the MDR-TB patient is having an adverse reaction to a specific, identifiable medication that is severe enough to preclude the further use of the medication (e.g., ototoxicity from streptomycin, gout from pyrazinamide, etc.), two treatment alternatives are available, depending upon the duration and success of treatment before the onset of the adverse reaction:

- The medication responsible for the adverse reaction may be omitted and the remainder of the anti-TB treatment regimen continued.

- A new, previously unused agent may be substituted for the offending medication. (This alternative does not increase the risk for drug resistance because the prior anti-TB treatment regimen was not failing).

If the cause for the adverse reaction (e.g., hepatotoxicity, skin rash) cannot be readily identified, all medications should be discontinued and retested by reintroduction singly into a regimen or trial. In some instances of severe toxicity, hospitalization for rechallenge with multiple drugs may be needed.

9. Aminoglycosides or capreomycin should be used for at least 6 months after culture conversion unless ototoxicity or nephrotoxicity develops. The continuation of aminoglycosides or capreomycin for longer than 6 months after culture conversion may be appropriate if there is extensive disease or slow conversion of sputum cultures. Authorities state the duration of treatment with an injectable medication is the strongest predictor of culture conversion and survival in patients with MDR-TB. With documented MDR-TB, overtreatment is far preferable to undertreatment, which may have dire consequences for the patient and his or her family.

10. Levofloxacin is the optically active L-isomer of ofloxacin. It is more active against *M. tuberculosis* than ofloxacin (which consists of equal amounts of the D- and L-isomers). The initial dose is 500 mg once daily. This dose could be increased over a 2-week period to 1000 mg given once daily.

    Levofloxacin should be used for the following patients:

    - All new patients who are candidates for fluoroquinolone therapy.

    - Patients currently on ciprofloxacin or ofloxacin could be changed to levofloxacin if they (1) are not responding to therapy, (2) have recently started fluoroquinolone therapy (within 3 months), or (3) are intolerant to the other fluoroquinolones.

    Those who have been on ciprofloxacin or ofloxacin for more than 3 months and are responding well to treatment can remain on those drugs.

    Levofloxacin has been associated with a decreased incidence of side effects compared to the older fluoroquinolones. In general, the adverse effects profile is similar to the other fluoroquinolones. It is a category C drug in pregnancy and should only be used if the potential benefit to the mother justifies the potential risk to the fetus.

11. Because the continued administration of second-line drugs may be life saving, physicians should not discontinue an anti-TB medication in a patient who has adverse reactions unless they are completely convinced that the medication is the cause of the reaction.

12. In general, any level of resistance to an anti-TB medication, documented by a reliable mycobacteriology laboratory, indicates that the drug is unlikely to be effective. However, susceptibility testing for pyrazinamide, ethionamide, and capreomycin is often inconsistent among laboratories or even within the same laboratory. In cases of partial resistance or inconsistent results, physicians should follow the general dictum of "use the medication, but do not depend on it for success."

13. Patients with isolated resistance to isoniazid at low concentrations (0.2 µg/ml) but susceptibility at high concentrations (1.0 µg/ml) may be treated with isoniazid (900 mg twice weekly) unless there are contraindications. The dictum of "use the medication, but do not depend on it for success" should also be applied in this situation. The regimen should include at least two, and preferably three, other drugs to which the strain is susceptible.

14. Most of the medications used to treat MDR-TB are known to cause fetal abnormalities or have not been studied adequately regarding their safety in pregnancy. Therefore, women of childbearing age who have MDR-TB should be strongly encouraged to use birth control methods if they are sexually active. Pregnant women with culture-proven MDR-TB should be offered abortion counseling.

V.B. Suggested Regimen for Specific Drug Resistance Patterns

The following suggested regimens should be considered guidelines only. In reality, the options are seldom clear-cut, as many patients will have already received trials of some of the medications, and may have had them added 1 at a time to previous regimens. Furthermore, opinions vary on the best medications to use for an individual patient. Expert consultation should be sought for individuals with confirmed or suspected MDR-TB.

1. ISONIAZID RESISTANCE (± STREPTOMYCIN RESISTANCE)

Regimen

- Use rifampin, pyrazinamide, and ethambutol for the duration of treatment. If the patient has extensive disease, consider adding a fourth agent — either a fluoroquinolone, an appropriate aminoglycoside, or capreomycin.

- If resistance to isoniazid (± streptomycin resistance) is discovered after the patient has been taking isoniazid, rifampin, pyrazinamide, and ethambutol for 1 to 3 months, and the patient has extensive disease requiring the addition of a fourth agent, a single medication can be added if the patient has responded to treatment and is smear negative for acid-fast bacilli. This does not violate the rule of "do not add a single drug to a failing regimen."

Length of treatment

- 6 months, or 4 months after culture conversion, whichever is longer.

If an aminoglycoside or capreomycin has been used, it may be discontinued 4 months after culture conversion. However, in patients with extensive disease or slow conversion of sputum cultures, the injectable should be used for 6 months after culture conversion.

2. RIFAMPIN RESISTANCE (± STREPTOMYCIN RESISTANCE)

Regimen

- Use isoniazid, pyrazinamide, and ethambutol, along with an appropriate aminoglycoside or with capreomycin. Use capreomycin or an aminoglycoside other than streptomycin if streptomycin resistance is known at the initiation of treatment.

Length of treatment

- HIV-seronegative patients without risk factors for HIV: 18 months after culture conversion.

- HIV-seropositive patients, other immunosuppressed patients, and patients with behavioral risk factors for HIV infection who decline HIV testing: 24 months after culture conversion.

In both situations, if an aminoglycoside or capreomycin has been used, it may be discontinued 4 to 6 months after culture conversion. However, in patients with extensive disease or slow conversion of sputum cultures, the injectable should be used for 6 months after culture conversion.

Surgery should be considered if a patient's cultures fail to convert to negative after 4 months of appropriate treatment (see Section V-L).

3. ISONIAZID AND ETHAMBUTOL RESISTANCE (± STREPTOMYCIN RESISTANCE)

Regimen

- Use rifampin, pyrazinamide, and a fluoroquinolone, along with an appropriate aminoglycoside or with capreomycin. Use capreomycin or an aminoglycoside other than streptomycin if streptomycin resistance is known at the initiation of treatment.

- If resistance to isoniazid and ethambutol (± streptomycin resistance) is discovered after the patient has been taking isoniazid, rifampin, pyrazinamide, and ethambutol for 1 to 3 months, discontinue isoniazid and ethambutol. Continue rifampin and pyrazinamide, and add at least a fluoroquinolone and possibly capreomycin or an appropriate aminoglycoside.

Length of treatment

- HIV-seronegative patients without risk factors for HIV: 9 to 12 months, or 6 months after culture conversion, whichever is longer.

- HIV-seropositive patients, other immunosuppressed patients, and patients with behavioral risk factors for HIV infection who decline HIV testing: 12 months, or 9 months after culture conversion, whichever is longer.

In both situations, the aminoglycoside or capreomycin may be discontinued 4 to 6 months after culture conversion to negative. However, in patients with extensive disease or slow conversion of sputum cultures, the injectable should be used for 6 months after culture conversion.

4. ISONIAZID AND RIFAMPIN RESISTANCE (± STREPTOMYCIN RESISTANCE)

Regimen

- Use pyrazinamide, ethambutol, and a fluoroquinolone, along with an appropriate aminoglycoside or with capreomycin, given daily five times a week. Use capreomycin or an aminoglycoside other than streptomycin if streptomycin resistance is known at the initiation of treatment.

- If resistance to isoniazid and rifampin (± streptomycin resistance) is discovered after the patient has been taking isoniazid, rifampin, pyrazinamide, and ethambutol for 1 to 3 months, discontinue isoniazid and rifampin. Continue pyrazinamide and ethambutol, and add to the regimen at least two drugs — a fluoroquinolone along with an appropriate aminoglycoside or with capreomycin.

- Most, but not all, *M. tuberculosis* strains that are resistant to rifampin are also resistant to rifabutin. However, a minority of rifampin-resistant organisms, especially those reported to be less than 50% resistant, will prove sensitive to rifabutin. When in vitro sensitivity to rifabutin is reported, add rifabutin to the regimen, along with the injectable and the other oral agents as outlined.

Length of treatment

- HIV-seronegative patients with noncavitary disease and no risk factors for HIV: 18 months after culture conversion.

- HIV-seropositive patients, other immunosuppressed patients, patients with behavioral risk factors for HIV infection who decline HIV testing, and patients with cavitary disease: 24 months after culture conversion.

In both situations, the aminoglycoside or capreomycin may be discontinued 6 months after culture conversion. In some patients, however, especially those with extensive disease or slow conversion of sputum cultures, the injectable should be used for longer than 6 months after culture conversion. Intermittent dosing for the injectable may be used after culture conversion.

- If in vitro sensitivity to rifabutin is reported and this drug is added to the regimen, treatment may be shortened to the duration of the same regimen with rifampin.

- Surgery should be considered if a patient's cultures fail to convert to negative after 4 months of appropriate treatment (see Section V-L).

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5. ISONIAZID, RIFAMPIN, AND ETHAMBUTOL RESISTANCE (± STREPTOMYCIN RESISTANCE)

Regimen

- Use pyrazinamide and a fluoroquinolone, along with an appropriate aminoglycoside or with capreomycin; *in addition,* use at least one, and ideally two, other second-line agents to which the strain is known or likely to be susceptible (e.g., ethionamide, cycloserine, or para-aminosalicylic acid [PAS]). Use capreomycin or an aminoglycoside other than streptomycin if streptomycin resistance is known at the initiation of treatment. Use rifabutin if rifabutin susceptibility has been documented.

- If resistance to isoniazid, rifampin, and ethambutol (± streptomycin resistance) is discovered after the patient has been taking isoniazid, rifampin, pyrazinamide, and ethambutol for 1 to 3 months, discontinue isoniazid, rifampin, and ethambutol. Continue pyrazinamide, and add to the regimen a fluoroquinolone, along with an appropriate aminoglycoside or with capreomycin, and two other agents to which the strain is known or likely to be susceptible.

Length of treatment

- HIV-seronegative patients with noncavitary disease and no risk factors for HIV: 18 months after culture conversion.

- HIV-seropositive patients, other immunosuppressed patients, patients with behavioral risk factors for HIV infection who decline HIV testing, and patients with cavitary disease: 24 months after culture conversion.

In both situations, the aminoglycoside or capreomycin may be discontinued 6 months after culture conversion. In some patients, however, especially those with extensive disease or slow conversion of sputum cultures, the injectable should be used for longer than 6 months after culture conversion. Intermittent treatment may be used after culture conversion.

- If in vitro sensitivity to rifabutin is reported and this drug is added to the regimen, treatment may be shortened to the duration of the same regimen with rifampin.

- Surgery should be considered if a patient's cultures fail to convert to negative after 4 months of appropriate treatment (see Section IV-L).

6. ISONIAZID, RIFAMPIN, AND PYRAZINAMIDE RESISTANCE (± STREPTOMYCIN RESISTANCE)

Regimen

- Use ethambutol, a fluoroquinolone, along with an appropriate aminoglycoside or with capreomycin; *in addition,* use at least one, and ideally two, other second-line agents to which the strain is known or likely to be susceptible.

- Use capreomycin or an aminoglycoside other than streptomycin if streptomycin resistance is known at the initiation of treatment. Use rifabutin if rifabutin susceptibility has been documented.

- If resistance to isoniazid, rifampin, and pyrazinamide (± streptomycin resistance) is discovered after the patient has been taking isoniazid, rifampin, pyrazinamide, and ethambutol for 1 to 3 months, discontinue isoniazid, rifampin, and pyrazinamide. Continue ethambutol, and consider increasing its dosage (25 mg/kg). Add to the regimen a fluoroquinolone, along with an appropriate aminoglycoside or with capreomycin, and two other agents to which the strain is known or likely to be susceptible (e.g., ethionamide and para-aminosalicylic acid [PAS]).

Length of treatment

- HIV-seronegative patients with noncavitary disease and no risk factors for HIV: 18 months after culture conversion.

- HIV-seropositive patients, other immunosuppressed patients, patients with behavioral risk factors for HIV infection who decline HIV testing, and patients with cavitary disease: 24 months after culture conversion.

In both situations, the aminoglycoside or capreomycin may be discontinued 6 months after culture conversion. In some patients, however, especially those with extensive disease or slow conversion of sputum cultures, the injectable should be used for longer than 6 months after culture conversion. Intermittent treatment may be used after culture conversion.

- If in vitro sensitivity to rifabutin is reported and this drug is added to the regimen, treatment may be shortened to the duration of the same regimen with rifampin.

- Surgery should be considered if a patient's cultures fail to convert to negative after 4 months of appropriate treatment (see Section IV-L).

7. ISONIAZID, RIFAMPIN, PYRAZINAMIDE, AND ETHAMBUTOL RESISTANCE (± STREPTOMYCIN RESISTANCE)

Regimen

- Use a fluoroquinolone, along with an appropriate aminoglycoside or with capreomycin; *in addition,* use at least two, and preferably three, other second-line agents to which the strain is known or likely to be susceptible. Use capreomycin or an aminoglycoside other than streptomycin if streptomycin resistance is known at the initiation of treatment. Use rifabutin if rifabutin susceptibility has been documented.

- If resistance to isoniazid, rifampin, pyrazinamide, and ethambutol **(**± streptomycin resistance) is discovered after the patient has been taking isoniazid, rifampin, pyrazinamide, and ethambutol for 1 to 3 months, discontinue all four drugs. Start a regimen of a fluoroquinolone, along with an appropriate aminoglycoside or with capreomycin, and at least two, and preferably three, other agents to which the strain is known or likely to be susceptible (e.g., ethionamide, cycloserine, and PAS).

Length of treatment

- HIV-seronegative patients with noncavitary disease and no risk factors for HIV: 18 months after culture conversion.

- HIV-seropositive patients, other immunosuppressed patients, patients with behavioral risk factors for HIV infection who decline HIV testing, and patients with cavitary disease: 24 months after culture conversion.

In both situations, the aminoglycoside or capreomycin may be discontinued 6 months after culture conversion. In some patients, however, especially those with extensive disease or slow conversion of sputum cultures, the injectable should be used for longer than 6 months after culture conversion. Intermittent treatment may be used after culture conversion.

- If in vitro sensitivity to rifabutin is reported and this drug is added to the regimen, treatment may be shortened to the duration of a regimen with rifampin.

- Surgery should be considered if a patient's cultures fail to convert to negative after 4 months of appropriate treatment (see Section IV-L).

8. ISONIAZID, RIFAMPIN, ETHAMBUTOL, STREPTOMYCIN, KANAMYCIN, AND RIFABUTIN RESISTANCE ("STRAIN W")

This resistance pattern should be suspected in patients who were hospitalized in an outbreak hospital, incarcerated within the New York State prison system since 1989, or had close contact with an individual who had this strain.

Regimen

- In patients suspected of having this strain, start with a regimen of isoniazid, rifampin, and pyrazinamide (in the event the strain is found to be susceptible to these medications), plus three other anti-TB medications to which the strain is likely to be susceptible. The three additional medications that have been used with apparent success are ciprofloxacin (or ofloxacin), cycloserine (in conjunction with vitamin B_6), and intramuscular or intravenous capreomycin.

- If this strain is confirmed, discontinue rifampin and treat with pyrazinamide, levofloxacin, cycloserine, and capreomycin. Two other anti-TB medications that may have a role in the treatment of this strain are PAS and clofazimine, although the anti-tuberculous activity of the latter is questionable. Empirically, do not use amikacin with this strain, as there is cross resistance to kanamycin. If necessary, use isoniazid intermittently at a high dosage (900 mg twice a week), because this strain is resistant only to low levels of isoniazid. However, do not rely on the effectiveness of isoniazid.

Length of treatment

- HIV-seronegative patients with noncavitary disease and no risk factors for HIV: 18 months after culture conversion.

- HIV-seropositive patients, other immunosuppressed patients, patients with behavioral risk factors for HIV infection who decline HIV testing, and patients with cavitary disease: 24 months after culture conversion.

In both situations, the aminoglycoside or capreomycin may be discontinued 6 months after culture conversion. In some patients, however, especially those with extensive disease or slow conversion of

sputum cultures, the injectable should be used for longer than 6 months after culture conversion. Intermittent treatment may be used after culture conversion.

- If in vitro sensitivity to rifabutin is reported and this drug is added to the regimen, treatment may be shortened to the duration of the same regimen with rifampin.

- Surgery should be considered if a patient's cultures fail to convert to negative after 4 months of appropriate treatment (see Section IV-L).

V.C. Sparfloxacin for Patients Who Are Failing MDR-TB Treatment

These are patients with MDR-TB who have persistently positive cultures after 3 to 6 months of treatment or who have radiographic worsening or convert to positive cultures after being negative for some months.

Sparfloxacin has 2 to 8 times greater mycobactericidal activity than ciprofloxacin, ofloxacin, or levofloxacin in tolerated doses. Sparfloxacin's activity has been compared with isoniazid. Quinolone resistance may develop less often than with ciprofloxacin or ofloxacin. Sparfloxacin is supplied as 200 mg tablets. The usual dose is a 400 mg loading dose followed by 200 mg once daily. It may be more effective at 400 mg once daily if tolerated. Adverse effects are generally similar to other quinolones except for two additional side effects.

- PHOTOTOXICITY. Sparfloxacin has been associated with a high incidence of phototoxicity. In some series, as many as 8% of patients suffered from this. The usual manifestations of phototoxicity have been erythema of the face and hands, sometimes of the trunk, with occasional blistering. In these studies the mean duration of the reaction has been 6.4 days (range 1-16) after discontinuation of the drug. Patients should be strongly advised to minimize direct sunlight exposure during the entire length of treatment and for at least 5 days after discontinuation of the drug — even through windows of houses or automobiles, because the harmful wavelengths are in the UVA range and are not absorbed by glass. They should be advised to be properly clothed (with hats, long sleeves, trousers, and socks) and wear an UVA-absorbing sunscreen on exposed skin areas if sunlight is unavoidable. Exposure to artificial UVA sources (tanning salons or UV therapy for skin diseases) must be avoided. Dark skin color may decrease the incidence of phototoxicity. All patients who are treated with sparfloxacin should be on directly observed therapy to recognize phototoxicity as early as possible.

- *TORSADES DE POINTES.* Sparfloxacin has also been associated with development of *torsades de pointes* in those receiving anti-arrythmics such as disopyramide and amiodarone. It is therefore contraindicated for individuals receiving these or other anti-arrythmics that cause prolongation of the QT interval. It is also not recommended for patients who are taking medications that can increase the QT interval (e.g., terfenadine, astemazole, erythromycin, ketoconazole, itraconazole, cisapride, or phenothiazines) or who may have hypokalemia or hypomagnesemia.

Because of the limitations of using this drug for a prolonged time, careful consideration should be given before starting a patient on sparfloxacin. Before a patient is started on this drug, the case should be discussed with The Medical Director. Its use should be limited to patients in the following categories:

- PATIENTS FAILING MDR-TB TREATMENT. They should be strong candidates for switching to sparfloxacin in addition to other anti-TB drugs if the strain is not fluoroquinolone resistant. Patients who had surgical lung resections for MDR-TB, especially with radiographic abnormalities of the remaining lung, may also be candidates for sparfloxacin.

- WEAK ANTITUBERCULOUS REGIMEN. Patients who are on "weak" antituberculous regimens (e.g., on clofazimine, ciprofloxacin, ethionamide, and cycloserine) are appropriate candidates for

sparfloxacin. Patients who are considered candidates for aminoglycosides but have contraindications to their use may also benefit from sparfloxacin.

- RESISTANCE TO MOST ANTITUBERCULOUS MEDICATIONS. One potential option of last resort is a combination of sparfloxacin and thiacetazone for 18 to 24 months if the patient's organism is susceptible to both.

V.D. Monitoring and Post-Treatment Evaluation

Patients being treated for drug-resistant TB should be monitored during treatment as outlined in Section VI. For information on adverse reactions and recommended regular monitoring for patients taking second-line anti-TB medications, see Section VI-B.

After completing treatment, patients with MDR-TB should be evaluated at 3, 6, 9, 12, 18, and 24 months.

VI. Monitoring and Follow-Up Evaluation for Tuberculosis Treatment

Content

VI.A. Monthly Clinical Evaluation

All Class III and Class V patients should receive monthly clinical evaluations by the physician and nurse to monitor their response to treatment, adherence to treatment, and adverse reactions.

Each monthly clinical evaluation should include the following:

1. VITAL SIGNS (to be performed by the public health assistant or nurse)

2. NURSE ASSESSMENT

The nurse is responsible for performing a monthly nursing assessment on the patient. Nurses should document the following items in the clinic medical record and inform physician of any untoward findings.

- Assessment of adherence
- Visual acuity testing and Ishihara color vision testing for patients taking ethambutol
- Monitoring of medication side effects
- Review of non-TB medications

3. PHYSICIAN ASSESSMENT

The following items should be assessed and/or discussed with the individual taking anti-TB treatment and noted in the clinic medical record:

SYMPTOMS AND SIGNS OF TB (RESPONSE TO TREATMENT)
All patients should be evaluated for symptoms and signs of TB during the physical examination. If symptoms persist despite treatment, nonadherence or drug resistance should be suspected and frequent sputum specimens should be obtained for culture and drug susceptibility testing. Patients who were initially culture negative should have a repeat chest x-ray and symptom review at 3 months to document response to treatment or to re-evaluate the possibility of nontuberculous lung disease.

ADHERENCE TO TREATMENT
The physician should review the directly observed therapy (DOT) records if the patient is receiving DOT. Patients not receiving DOT should be instructed to bring in all anti-TB medication bottles and the physician or nurse should count the pills.

All patients should be directly questioned about when and how they take the medications. Also, they should be asked to describe the appearance of the medications and the number of pills they take each day. Laboratory tests may be done to detect increased uric acid levels in patients taking pyrazinamide.

MEDICATION SIDE EFFECTS
Specific medications and their side effects should guide the physician's decision regarding the physical exam and laboratory evaluation. (See Table VI-1.) During treatment with ethambutol, visual acuity and color vision must be monitored monthly. Each eye should be checked separately. Ethambutol should be discontinued as soon as susceptibility to isoniazid and rifampin is documented. For information on monitoring side effects to aminoglycosides or capreomycin, see Section VI-B(9).

PHYSICAL EXAMINATION
The nature and extent of the physical exam depends on the patient's symptoms and site of disease (e.g., evaluation of lymph node size, medication side effects).

ASSESSMENT OF PREVIOUS SPUTUM AND OTHER LABORATORY TESTS, AND DECISIONS MADE BASED ON RESULTS
Patients should be informed about whether their tests show an improvement in or a deterioration of their condition.

LABORATORY EVALUATION
Induced sputum should be ordered monthly for AFB smear and culture. Susceptibility testing on the most recent positive *M. tuberculosis* culture should be requested if cultures remain positive after 4 months of treatment, or if the individual fails to improve clinically.

Baseline liver function tests (LFTs) and a complete blood count, including platelets, should be done for all patients. Serial LFTs should be done monthly or more often if (1) the baseline laboratory values were elevated above the normal range, (2) the patient is suspected on the basis of history or physical exam to have liver disease, (3) the patient has a risk factor for liver disease, such as alcoholism, HIV infection, pregnancy, or postpartum condition, or (4) the patient is being treated with second-line medications that may be hepatotoxic (e.g., ethionamide) or with medications that may be hepatotoxic but are unrelated to TB treatment.

Other relevant laboratory values should be obtained at appropriate intervals according to the medications used and any side effects present. For example, the aminoglycosides and capreomycin may affect renal function and hearing; uric acid values are affected by pyrazinamide. (Note: an increase in uric acid is not an indication to discontinue pyrazinamide, as long as the patient remains asymptomatic.)

NOTATION OF A PLAN OF CARE BASED ON EVALUATION OF CURRENT STATUS
Because several medical providers may be involved in the care of one patient, it is important to outline a plan of care that delineates reasons for decisions, names and dosages of medications, planned length of treatment, etc.

REORDERING OF MEDICATIONS (TO BE WRITTEN ON THE MEDICATION ORDER SHEET)
To prevent errors, abbreviations should not be used on the medication order sheet.

REVIEW OF NON-TB MEDICATIONS
All medications that patient is taking must be reviewed with the patient and noted in his or her medical record at each clinic visit. In addition, a patient must be notified of potential drug interactions to any anti-TB medications that are prescribed in Pulmonary Disease Services.

If there has been no change in the use of non-TB medications from previous visit(s), the documentation in the medical record should read: "no change in medication status." If the patient reports using new medications, if there has been a change in dosage, or if any medications have been discontinued, the physician should (1) enter the name and dosage of the medication(s) in the clinic medical record, (2) determine whether the new non-TB medication(s) might interact with the anti-TB medications the patient is currently taking, and (3) discuss potential drug interaction(s) with the patient and document this discussion in the clinic medical record. New orders are written at each patient visit.

VI.B. Management of Adverse Reactions

Anti-TB medications can cause a variety of adverse reactions, summarized in Table VI-1.

1. DERMATITIS

HISTORY AND EXAMINATION
- The patient should be questioned about exposure to other medications or skin preparations, environmental contact, etc. that may be responsible.

- HIV-seropositive patients are subject to a variety of dermatologic diseases either directly or indirectly related to HIV infection, or to other medications used for therapy or prophylaxis. Consultation with an appropriate infectious disease service or dermatology clinic may be required.

- The patient should be carefully examined for evidence of unrelated skin disease (scabies, contact dermatitis, childhood exanthem, acne, etc.).

FOLLOW UP

- If the dermatologic reaction is severe and no other cause is found, anti-TB medications should be discontinued promptly and the patient should be examined each week until the skin reaction disappears.

- Patients with a severe dermatologic reaction (e.g., exfoliative dermatitis) or dermatitis associated with severe systemic reactions should be referred for hospital admission for treatment and the establishment of a new anti-TB regimen or a rechallenge regimen, under daily surveillance as an inpatient.

RESTARTING ANTI-TB MEDICATIONS

- In cases managed in the clinic, it is appropriate to rechallenge after the skin reaction clears or subsides. It may not be possible to identify the specific causative agent by the characteristics of the skin reaction. Thus, it is appropriate to restart the most important member of the regimen (either isoniazid or rifampin) first, before trying pyrazinamide or ethambutol. (Note: In at least one study, pyrazinamide was found to be a major cause of skin reactions, and most reactions were found to occur within the first 4 weeks of treatment.[1])

- Single daily doses of isoniazid or rifampin should be given alone for 3 days with instructions to discontinue promptly if a reaction recurs. The patient should be examined in 3 to 4 days.

    - If there is no reaction, the alternate drug, rifampin or isoniazid, should be added with similar instructions. The patient should be reexamined in 3 to 4 days.

    - If the skin reaction does not recur or if it is not severe, ethambutol should be added (if this drug was part of the initial regimen). If there is no reaction to ethambutol, the regimen of isoniazid, rifampin, and ethambutol can be continued and pyrazinamide deleted on the presumption that this caused the skin reaction.

- Treatment should be continued with the original regimen, minus the causative agent. A longer period of treatment may be required if the causative agent was isoniazid or rifampin, or pyrazinamide during the initial 2 months of treatment. For patients who are HIV seropositive or who have extensive pulmonary or disseminated TB, a new single drug, such as streptomycin or a fluoroquinolone, should be added to regimens that lack isoniazid or rifampin (see Section V). The new drug should be continued for the duration of therapy. (In such instances, the addition of a single agent to a successful regimen does not violate the rule of "do not add a single drug to a failing regimen.")

TABLE VI-1

Common Adverse Reactions to First-Line Anti-TB Medications

Adverse Reaction	Symptoms and Signs	Usual Causes
Dermatitis	itching, rash, hives, fevers, etc.	rifampin, pyrazinamide, isoniazid, rarely ethambutol
Hepatitis	anorexia, nausea, vomiting, jaundice	isoniazid, rifampin, pyrazinamide, rarely ethambutol
Gastritis	anorexia, nausea, vomiting, epigastric pain	rifampin, pyrazinamide
Peripheral neuropathy	numbness or paresthesias of feet or hands	isoniazid
Joint manifestations	gout-like manifestations manisfestations like systemic lupus erythematosus	pyrazinamide, isoniazid
Renal manifestations	hematuria, azotemia	rifampin, aminoglycosides
Hematologic manifestations	leukopenia, other thrombocytopenia	isoniazid, rifampin, pyrazinamide, ethambutol
Visual manifestations	vision loss and color blindness	ethambutol
Audiovestibular manifestations	hearing loss, vertigo, new-onset tinnitus	aminoglycosides, capreomycin

The same principles of management apply to patients who experience dermatologic reactions while taking “retreatment" regimens for multidrug-resistant TB.

2. HEPATITIS (DRUG RELATED)

HISTORY AND EXAMINATION

- Individuals taking anti-TB medication(s) who develop symptoms consistent with hepatitis (anorexia, nausea, vomiting, abdominal pain, and jaundice) should be instructed to discontinue all medications promptly. These patients should be examined by a physician and have liver function tests (LFTs).

- In some patients, rifampin or pyrazinamide may cause gastritis with symptoms similar to those of hepatitis. In these patients, LFTs remain normal or stable despite symptoms. See Section VII-B(3).

FOLLOW UP

- If symptoms disappear promptly and LFTs are normal, drug-induced hepatitis is unlikely. Another cause for symptoms should be suspected; depending upon the nature, duration, and severity of symptoms, a decision should be made regarding further diagnostic investigation.

- If the LFTs are abnormal (SGOT/AST or SGPT/ALT is >5 times the upper limit of normal) or if serum bilirubin is elevated, with or without symptoms, drug-related hepatitis should be strongly suspected and all anti-TB medication(s) should be discontinued.

- The patient should be examined and have LFTs repeated at least weekly. If symptoms persist for more than 2 weeks without anti-TB medication(s), or if LFTs continue to worsen, the physician should suspect progressive drug-related hepatitis or an unrelated cause of hepatitis. Depending upon the severity of the hepatitis, indicated by clinical findings and LFTs, hospitalization may be necessary for closer observation and therapy.

- As soon as hepatitis is identified, a viral hepatitis profile should be requested.

RESTARTING ANTI-TB MEDICATIONS

- If there is strong evidence that the symptoms are not related to anti-TB medication(s), the entire regimen should be reinstituted promptly and the individual followed closely for the recurrence of symptoms.

- If the patient has extensive pulmonary or disseminated TB, has HIV infection, or lives in a congregate setting or with young children or immunosuppressed persons, the institution of a new regimen with a lesser potential for hepatotoxicity (e.g. streptomycin, ethambutol, fluoroquinolone) may be indicated even before liver enzymes return to normal.

- For all other patients, anti-TB treatment should be withheld until symptoms disappear and LFTs are normal or have declined and "plateaued." During this time, the patient should be followed closely with weekly LFTs. It is then appropriate to rechallenge with a single daily dose of one of the drugs in the prior regimen.

- If hepatitis is caused by any one of the drugs in the anti-TB regimen, isoniazid is most likely to be responsible, followed by pyrazinamide, rifampin, and ethambutol (in this order).

- Although the specific cause of hepatitis cannot be identified by the pattern of LFT abnormality, rifampin is usually implicated if the pattern is cholestatic (bilirubin and alkaline phosphatase elevated and out of proportion to enzyme elevations). In contrast, isoniazid, rifampin, or pyrazinamide may be the cause if the pattern is hepatocellular, with enzymes elevated and out of proportion to bilirubin or alkaline phosphatase. Ethambutol very rarely causes hepatitis.

- *Cholestatic pattern.* If the initial pattern of hepatitis is cholestatic, the patient should be rechallenged with a standard daily dosage of isoniazid and ethambutol after LFTs return to normal or decline and plateau. The patient should be examined weekly at each visit.

- If LFTs remain stable after one week of isoniazid and ethambutol and the patient is asymptomatic, pyrazinamide should be added to the regimen. If there are no subsequent signs of hepatotoxicity, rifampin-induced hepatitis should be assumed, and the patient should be treated with isoniazid, ethambutol, and pyrazinamide. Capreomycin or an appropriate aminoglycoside, as well as a fluoroquinolone, should be considered for the regimen (see Section IV-E).

- *Hepatocellular pattern.* If the pattern is hepatocellular, it is appropriate to rechallenge first with the agent least likely to have been responsible — that is, ethambutol alone for a period of one week — after LFTs return to normal or decline and plateau. The patient should be instructed to stop the medication immediately if symptoms of hepatitis occur. The patient should be examined weekly, with LFTs repeated at each visit.

- If LFTs remain stable after 1 week of ethambutol and the patient is asymptomatic, rifampin should be added at the usual dosage, and ethambutol continued. The patient should be followed carefully at weekly intervals as before.

    - If LFTs remain stable after 1 week of ethambutol and rifampin, pyrazinamide should be added to the regimen of ethambutol and rifampin. If there are no subsequent signs of hepatotoxicity, isoniazid-induced hepatitis should be assumed, and the patient should be treated with ethambutol, rifampin, and pyrazinamide.

    - If LFTs worsen after 1 week of ethambutol and rifampin, these medications should be stopped. LFTs should be allowed to return to normal or to decline and plateau, and then the patient should be rechallenged with isoniazid and ethambutol.

    - If LFTs remain stable after 1 week of isoniazid and ethambutol, pyrazinamide should be added to the regimen. If there are no subsequent signs of hepatotoxicity, rifampin-induced hepatitis should

be assumed, and the patient should be treated with isoniazid, ethambutol, and pyrazinamide. Capreomycin or an appropriate aminoglycoside, as well as a fluoroquinolone, should be considered for the regimen (see Section IV-E).

A suggested algorithm for restarting anti-TB medications in patients with drug induced hepatitis is presented in Figure VI-1.

Patients who start treatment with a new regimen because of hepatitis should have monthly LFTs for the remainder of treatment.

- Individuals who cannot take either isoniazid or rifampin should be treated with a "retreatment regimen" — usually pyrazinamide, ethambutol, and a fluoroquinolone, along with an appropriate aminoglycoside or with capreomycin, given for 18 to 24 months. (See Section IV-E)

- Similar principles of management apply to cases of hepatitis induced by "retreatment drugs," e.g., ethionamide, para-aminosalicylic acid (PAS), rifabutin, and rarely fluoroquinolones.

3. GASTRITIS

Almost any medication can cause gastric irritation in susceptible individuals. Of the first-line anti-TB medications, rifampin most often causes gastritis, although pyrazinamide is responsible in some instances. Because rifampin is the most important member of combined chemotherapy, every effort should be made to reintroduce this drug without the recurrence of gastric symptoms.

HISTORY AND EXAMINATION

- Because the symptoms of gastritis (anorexia, nausea, vomiting, and epigastric distress) may be due to drug-related hepatitis, LFTs must be done on all individuals who present such symptoms.

FOLLOW UP

- Anti-TB medications should be discontinued in symptomatic patients. If LFTs are normal or unchanged from baseline, and symptoms persist for 4 to 5 days without medication, unrelated gastrointestinal disease (e.g., peptic ulcer disease, gastritis due to another cause, etc.) should be suspected and appropriate referral made for diagnostic investigation.

RESTARTING ANTI-TB MEDICATIONS

- If the individual is taking isoniazid, rifampin, pyrazinamide, and ethambutol, rifampin is the most likely cause of gastric symptoms. After symptoms subside, it is appropriate to renew treatment with isoniazid, pyrazinamide, and ethambutol.

- If gastric symptoms return, pyrazinamide should be suspected as the cause, and treatment should be attempted with isoniazid, rifampin, and ethambutol.

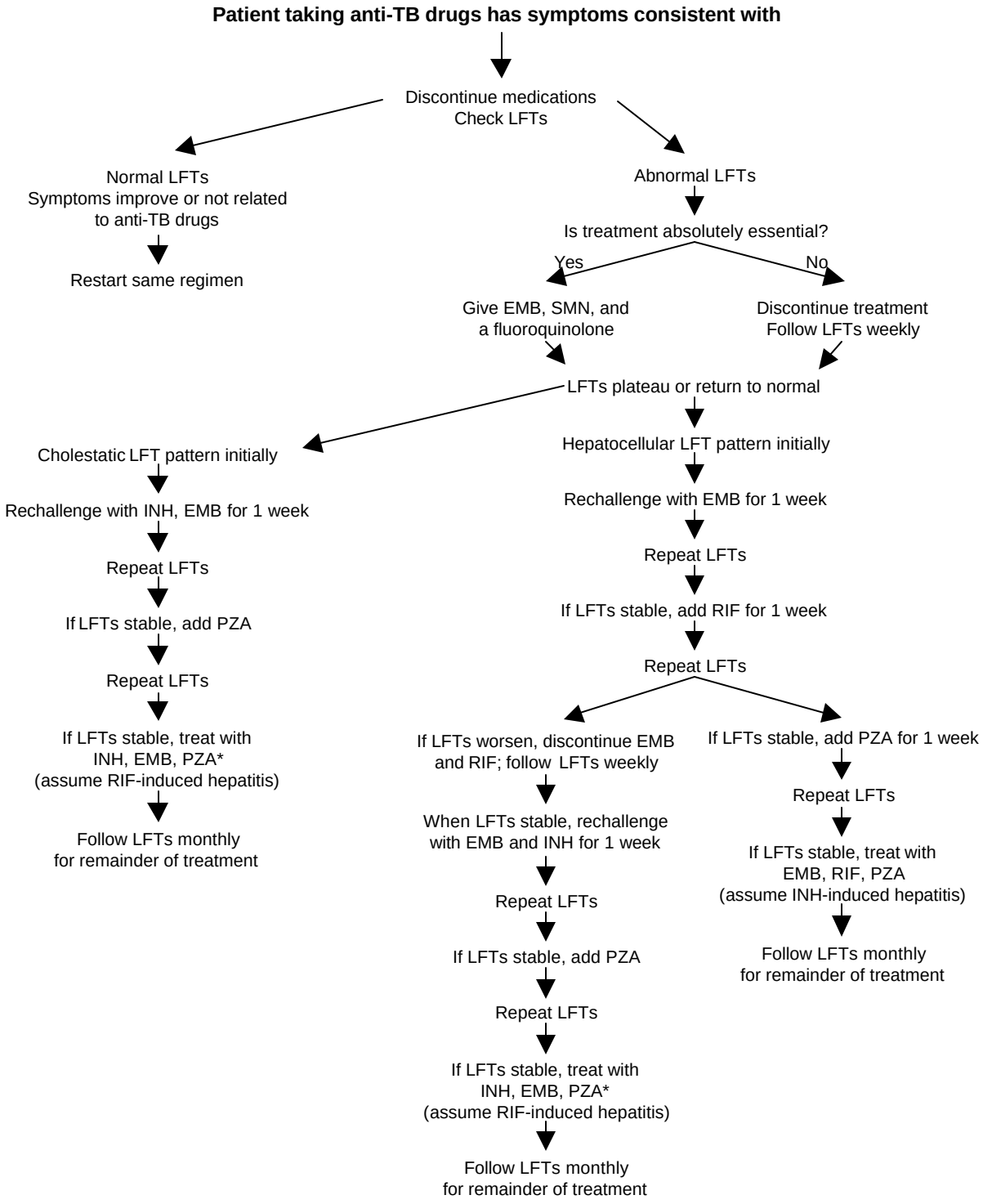
- If symptoms do not recur, rifampin may be introduced in most cases without the recurrence of gastric symptoms by modifying the pattern of administration: example, giving all of the medication before bedtime, preceding the medication with a small meal, or renewing rifampin with a smaller dose (300 mg) and increasing to 600 mg over a period of 1 to 2 weeks.

- Antacids may be useful to help alleviate the symptoms of gastritis, but antacids may interfere with the absorption of isoniazid and quinolones. When employed, antacids should be given 1 to 2 hours after isoniazid has been taken; prolonged use should be avoided.

- If gastritis is caused by pyrazinamide, this drug can be omitted from the regimen with less risk than with rifampin. If the patient has TB susceptible to isoniazid and rifampin, he or she can be treated with these 2 medications for a total of 9 months (12 months if HIV seropositive).

FIGURE VI-1

Suggested Algorithm for Restarting Anti-TB Medications in Patients with Drug-Induced Hepatitis



* Capreomycin or an appropriate aminoglycoside, as well as a fluoroquinolone, should be considered for the regimen (see Section IV-E)

4. PERIPHERAL NEUROPATHY

Isoniazid may cause peripheral neuropathy, especially in individuals with a predisposing cause, such as alcoholism, diabetes, HIV infection, or malnutrition. Pyridoxine usually, but not invariably, prevents the emergence of isoniazid-induced peripheral neuropathy. In rare instances, ethambutol can also cause peripheral neuritis.[2]

HISTORY AND EXAMINATION

- Isoniazid should be assumed to be the primary cause for paresthesias and numbness of the feet and hands, with or without peripheral motor weakness, in isoniazid-treated patients, even if other predisposing causes are present.

FOLLOW UP

- Isoniazid should be discontinued in patients with peripheral neuritis, and large doses of pyridoxine should be given.

- The neuropathy usually subsides when it is diagnosed early and isoniazid is promptly discontinued. However, neurologic injury may be irreversible if the diagnosis is delayed and the manifestations become severe. Neurologic consultation should be obtained if the diagnosis is not clear.

5. JOINT MANIFESTATIONS

- Isoniazid can induce active systemic lupus erythematosus (SLE), especially in patients who have this disease in a subclinical stage. The patient may have only arthralgias or alopecia or may present a full-blown pattern of SLE, with arthritis and other systemic manifestations. The diagnosis requires clinical suspicion and positive antinuclear antibody (ANA) markers of SLE. Isoniazid must be discontinued, and these patients should be referred to an appropriate medical or rheumatology clinic.

- Pyrazinamide invariably leads to increase levels of serum uric acid because it impairs renal excretion of uric acid. In rare situations, elevated serum uric acid induces typical bouts of gouty arthritis, especially in patients with a history of gout. Pyrazinamide should be discontinued in such instances, unless it is essential to the anti-TB regimen. Allopurinol can lower the baseline serum uric acid level, but it cannot lower serum uric acid levels that are elevated because of pyrazinamide.

- Hyperuricemia without symptoms of gout is not a reason for discontinuing pyrazinamide.

6. RENAL MANIFESTATIONS

Renal injury in patients treated for TB is most often due to aminoglycosides or capreomycin. Also, rifampin can cause acute or chronic nephritis (with or without symptoms), evidenced by proteinuria, hematuria, and urinary white blood cells. In rare instances, acute or chronic renal failure can occur. Isoniazid, pyrazinamide, and ethambutol are not known to cause renal disease, although the blood levels of ethambutol (and cycloserine, aminoglycosides, and capreomycin) may become markedly elevated in patients with renal function impairment.

HISTORY AND EXAMINATION

- Urinalysis, blood urea nitrogen, and creatinine should be monitored serially in patients with underlying renal disease who are taking ethambutol, cycloserine, or an aminoglycoside. Similar studies should be done promptly in any patient who has symptoms consistent with acute or chronic nephritis.

FOLLOW-UP

- For information on treatment and follow-up in patients with chronic renal failure, see Section IV-E.

7. HEMATOLOGIC MANIFESTATIONS

All first-line anti-TB agents can, in rare cases, lead to hematologic abnormalities. Rifampin is the most common cause of thrombocytopenia, although the other first-line drugs may depress platelets as well. A “flu-like syndrome" has been reported with rifampin, especially when it is used intermittently. This is an acute episode with fever, chills, and muscle pain that may be associated with severe anemia, thrombocytopenia, and leukopenia. Rifampin, isoniazid, pyrazinamide, and rarely, ethambutol can cause leukopenia. Hemolytic syndromes and other types of anemia are rarely encountered.

EXAMINATION AND FOLLOW-UP

- If a patient taking anti-TB drugs develops symptoms, signs, or laboratory evidence of significant anemia, leukopenia, or thrombocytopenia that cannot otherwise be explained, all anti-TB drugs should be discontinued. The patient should be referred promptly for hematologic consultation.

8. VISUAL MANIFESTATIONS

Ethambutol-induced optic neuritis occurs only rarely, and usually regresses completely when ethambutol is discontinued. However, optic neuritis may progress to severe visual loss if diagnosed late. In general, optic neuritis occurs mostly with elevated serum levels of ethambutol; because the drug is cleared largely by renal excretion, individuals with impaired renal functions are most susceptible, as are patients given doses of ethambutol larger then 15 mg/kg body weight.

HISTORY AND EXAMINATION

- The usual symptoms of optic neuritis are loss of visual acuity for small objects (newsprint, sewing, etc.) and/or impairment of red-green color discrimination.

- Ethambutol should be avoided, or used with caution and with frequent monitoring of vision and renal function, in patients (1) with renal function abnormalities, (2) at risk for renal function abnormalities (e.g., elderly patients and patients with diabetes or hypertension), and (3) patients with pre-existing, non-correctable loss of vision. All patients at risk for renal disease should have serum blood urea nitrogen and creatinine tested before treatment with ethambutol. Also, baseline visual acuity and red-green color discrimination should be established at the initiation of therapy. Serial tests of visual acuity and color vision are indicated for early detection of signs of optic neuritis; in addition, the patient should be asked about visual changes at each follow-up visit.

FOLLOW UP

- Ethambutol should be discontinued immediately if optic neuritis is suspected, and the patient should be referred for ophthalmology consultation if the visual impairment does not reverse promptly. In some patients, visual impairment due to ethambutol may take months to resolve.

9. AUDIOVESTIBULAR MANIFESTATIONS

HISTORY AND EXAMINATION

- Patients receiving an aminoglycoside or capreomycin should have a baseline audiogram and a follow-up audiogram during the first and second months of treatment. The audiogram should be repeated every 2 months thereafter. In addition, the audiogram should be repeated promptly if hearing loss is suspected.

- At each monthly examination, patients receiving an aminoglycoside or capreomycin should be asked about changes in hearing. Most patients will volunteer information about tinnitus or dizziness if these symptoms occur.

FOLLOW UP

- The aminoglycoside or capreomycin should be discontinued if hearing loss, vertigo, or new-onset tinnitus occurs. A careful ear examination should be done to exclude other sources of these symptoms, such as cerumen or otitis media.

- An audiogram should be performed and the results compared with the baseline results in order to detect hearing loss.

- If symptoms or any other evidence of hearing loss is suspected to be unrelated to the aminoglycoside or capreomycin, the patient should be referred to an otolaryngology clinic for consultation.

RESTARTING ANTI-TB MEDICATIONS

- If significant hearing loss, new-onset tinnitus, or vertigo is demonstrated and any of these reactions cannot be explained otherwise, the aminoglycoside or capreomycin should be eliminated from the regimen.

VI.C. Reclassification of TB Class V Patients (see page iv)

All patients initially classified as TB Class V should be reclassified to the appropriate TB class within 4 months of the initiation of anti-TB treatment.

Patients initially classified as TB Class V should be reclassified as TB Class III if they have a positive *M. tuberculosis* culture.

- Patients initially designated as TB Class V who do not produce a positive culture for *M. tuberculosis* should be reclassified as TB Class III if they meet the following criteria:

  - Resolution of TB symptoms (e.g. cough, fever, sweats, weight loss, chest pains), if initially present, in a time course consistent with TB

  - Improvement of chest x-ray (e.g., improvement or resolution of infiltrates, cavities, and effusions) in a time course consistent with TB

- Patients initially designated as TB Class V who are found to have a negative culture for *M. tuberculosis* should be reclassified as TB Class IV if their chest x-ray is stable after 4 months of treatment. A non-TB diagnosis should also be considered.

- Patients may only be considered Class III when they are classified as "countable" on the Tuberculosis Registry.

VI.D. Case Closing and End-of-Treatment Evaluation

- At the end of treatment for pulmonary TB, one sputum culture and a chest x-ray should be ordered.

- All patients who complete treatment, except those requiring post-treatment evaluations (see Section VI-E), should be discharged from the clinic and provided a treatment completion record.

- In patients who have been lost to follow-up but whose cultures have converted to negative, the TB case may be closed as "treatment complete" (for surveillance purposes) if the patient has completed a specific number of months of treatment:

VI.E. Post-Treatment Evaluation

Controlled trials of TB treatment have demonstrated conclusively that the risk of relapse is low in patients with TB susceptible to isoniazid, rifampin, and pyrazinamide who complete an optimal treatment regimen. Post-treatment evaluation of patients in this category, therefore, is rarely productive and is not cost-effective. These patients, however, should be advised to return to the clinic for reevaluation if, in the future, they develop symptoms suggestive of active pulmonary TB (e.g., fever, night sweats, weight loss, malaise, or prolonged cough, with or without sputum).

Post-treatment evaluation is also not required for most patients who (1) have *M. tuberculosis* isolates resistant to isoniazid only but susceptible to rifampin, pyrazinamide, and ethambutol and (2) have completed 6 months of treatment with all three medications, with or without a quinolone. Controlled trials have shown low relapse rates for these patients, comparable to rates for patients with isoniazid-susceptible strains.

The recommendations for the frequency of post-treatment evaluation are summarized in Table VI-2.

1. CANDIDATES AND PROCEDURE FOR POST-TREATMENT EVALUATION: CATEGORIES A AND B

Certain patients are at greater risk for post-treatment relapse and should be reevaluated periodically after they complete treatment. Patients in this category include the following:

A. Patients with TB resistant to isoniazid and rifampin, regardless of the regimen used and the duration of treatment

B. Patients treated with a regimen that did not include rifampin or rifabutin because of resistance or adverse reactions to these drugs

Patients in categories (a) and (b) above should be scheduled to return for reevaluation at 3, 6, 9, 12, 18 and 24 months (i.e., 6 visits total). A chest x-ray should be obtained at each visit and compared with the chest x-ray obtained at the end of therapy. At each visit, a single sputum specimen should be obtained for smear and culture. A second appointment is not needed to present the results of the culture, but patients should be told that they would be contacted by telephone if the results were positive.

If the smear is positive for acid-fast bacilli, the patient should be advised to return for three additional sputum specimens. If any specimen is culture positive for *M. tuberculosis,* the patient should return promptly for a complete clinical reevaluation and the reinstitution of appropriate therapy.

2. CANDIDATES AND PROCEDURE FOR POST-TREATMENT EVALUATION: CATEGORIES C. D. AND E

Patients in the following categories should also receive periodic post-treatment evaluation:

C. Patients who were treated with a self-administered regimen

D. Selected patients who have a history of previous treatment, but who (1) have no details available about the treatment, (2) have negative sputum cultures, (3) have significant changes on the chest x-ray, and (4) refuse preventive retreatment

E. Selected patients, who have no history of previous treatment and who (1) have negative sputum cultures, (2) have significant changes on the chest x-ray, and (3) refuse preventive treatment

Patients in categories (C), (D, and (E) should be reevaluated as described for categories (A) and (B), but only at 3, 6, and 12 months.

TABLE VI-2

Frequency of Post-Treatment Evaluation

Category of Patient	Frequency of Post-Treatment Evaluation
A. Patients with TB resistant to INH and RIF	Every 3, 6, 9, 12, 18 and 24 months*
B. Patients treated without RIF or rifabutin	Every 3, 6, 9, 12, 18 and 24 months*
C. Selected patients treated with a self-administered regimen whose adherence to therapy is in doubt	At 3, 6, and 12 months*
D. Selected patients who have a history of previous treatment, but who (1) have no details available about the treatment, (2) have negative sputum cultures, (3) have significant changes on the chest x-ray, and (4) refuse preventive retreatment	At 3, 6, and 12 months*
E. Selected patients who have no history of previous treatment and who (1) have negative sputum cultures, (2) have significant changes on the chest x-ray, and (3) refuse preventive retreatment	At 3, 6, and 12 months*
F. Selected patients who are TST positive and culture negative and who are treated empirically because the chest x-ray may be consistent with TB but also with pulmonary disease other than TB	Refer to general chest clinic if no response to treatment and diagnosis is not clear
Patients with pan-susceptible TB who complete an optimal regimen	No reevaluation necessary
Most patients who have monoresistance to INH but who complete 6 months of treatment with at least RIF, pyrazinamide, and ethambutol	No reevaluation necessary

* INH = isoniazid RIF = rifampin

- Evaluation should include a chest x-ray and the collection of a sputum specimen for smear and culture.

3. CANDIDATES AND PROCEDURE FOR POST-TREATMENT EVALUATION: CATEGORY F

F. Comprises patients who have a positive tuberculin skin test reaction, who have negative sputum cultures for TB, and who are treated empirically because a lesion apparent on the chest x-ray is believed consistent with TB. There is always a possibility that the lesion is not the result of TB infection but is caused by some other disease. This problem is especially pertinent when the lesion is a non-calcified spherical lesion, a “segmental” shadow consistent with bronchial obstruction, or enlarged hilar or mediastinal nodes of unproven cause. In such circumstances, patients who have no clear-cut response to anti-TB therapy should be referred to a general chest clinic for additional diagnostic investigation.

4. SPECIAL CONSIDERATIONS FOR HIV-SEROPOSITIVE PATIENTS

Whenever possible, every HIV-seropositive TB HIV patient who has been treated should be followed at the same time by an appropriate clinic; those patients who are not attending an HIV disease clinic should be urged to seek care for their HIV disease as soon as possible.

5. THE USE OF ISONIAZID AFTER COMPLETION OF ANTI-TB TREATMENT

The policy of the Orange County Health Care Agency Pulmonary Disease Services is not to use single-drug prophylaxis after the completion of TB treatment. This policy includes patients who are HIV seropositive.

References

1. Ormerod LP, Horsfield N. Frequency and type of reactions to antituberculosis drugs: observations in routine treatment. *Tubercle and Lung Disease.* 1996;77:37-42.

2. Tugwell P, James SL. Peripheral neuropathy with ethambutol. *Postgraduate Medical Journal* 1972;48:667-670.

VII. Infection Control

Contents

VII.A. Discharge from Acid-Fast Bacilli (AFB) Isolation

In most cases, TB can be treated entirely in an outpatient setting. Many individuals, however, have at least part of their treatment in the hospital under AFB isolation. Any individual admitted to the hospital and suspected of having AFB smear-positive pulmonary or laryngeal TB should be placed in an AFB isolation room initially. (AFB isolation is defined as a room that has negative air pressure relative to the hall and 12 or more air exchanges per hour, of which at least 2 exchanges are outside air.[1])

Patients in AFB isolation may be transferred to a non-isolation hospital bed or they may be discharged from the hospital directly. Because other hospitalized individuals may be especially vulnerable to TB infection, the criteria for transferring smear-positive patients from isolation to a non-isolation bed may be more restrictive than the criteria for discharging smear-positive patients from the hospital. For example, an individual must be smear negative to be considered for transfer from isolation, but not necessarily for discharge from the hospital.

1. TRANSFER TO A NON-ISOLATION HOSPITAL BED

Patients may be considered for transfer from AFB isolation to a non-isolation hospital bed when they demonstrate both bacteriologic and clinical evidence of response to anti-TB treatment. Based on guidelines of Centers for Disease Control and of the California Tuberculosis Control Association, patient must meet all three of the following criteria:

- The resolution of fever and the resolution, or near resolution, of cough
- Current treatment with an appropriate anti-TB regimen to which the strain is known or likely to be susceptible for at least 2 weeks
- Three consecutive negative AFB smears from sputum specimens taken on different days.

The decision to transfer a patient from AFB isolation to a non-isolation hospital bed must be made by the hospital staff. Patients transferred to a non-isolation room should have a sputum specimen collected for AFB smear at least every 2 weeks during their hospitalization, or sooner if TB symptoms recur.

{atients suspected of having or known to have multidrug-resistant TB (MDR-TB) should remain in an isolation room throughout their hospitalization. Patients with pan-susceptible TB who are hospitalized for reasons unrelated to TB should be isolated until their infectiousness has been assessed.

2. DISCHARGE FROM THE HOSPITAL

The determination if a patient is medically stable for discharge must be made by the hospital staff. Approval of the discharge plan by the TB Controller is referred prior to discharge or transfer to a lower level of care.

The following criteria are recommendations of the Orange County Health Care Agency Pulmonary Disease Services; California State Department of Health Services has the responsibility and the authority for regulating hospitals. The decision to discharge from the hospital an individual who is smear positive for AFB must be made by the hospital staff. Consultation with Orange County Health Care Agency Pulmonary Disease Services, TB Discharge Planner is required.

Except for discharge to high-risk environments, there is no minimum number of days of anti-TB treatment that is required before a patient may be discharged from the hospital. Smear-positive patients who are not suspected of having multidrug-resistant TB and who are well enough to be discharged from the hospital may be discharged if they meet all three of the following criteria:

- The resolution of fever and the resolution, or near resolution, of cough
- Current treatment with an anti-TB regimen to which the strain is known or likely to be susceptible
- Confidence on the part of the staff that the patient will adhere to anti-TB treatment given by directly observed therapy, after discharge from the hospital
- Smear-positive patients should not be discharged to one of the living situations listed in Section VII-A(3).

Smear-positive patients who are still symptomatic but are (1) currently receiving appropriate treatment and (2) likely to adhere to treatment may be considered for discharge from the hospital if they meet all three of the following criteria:

- They live alone or are going back to a living environment where others are immunocompetent and wish to have them home (the most infectious period has passed)
- They are willing, able, and motivated to cover their mouth when coughing
- They will not have significant contact (including living in the same household) with infants, young children, or immunosuppressed persons, and they will not be receiving social services in which the provider (e.g., home attendant) will be routinely seeing them for several hours at a time

Smear-positive patients who are suspected of having pulmonary MDR-TB should remain in the hospital (in AFB isolation) until they meet all three of the following criteria:

- They have three consecutive negative AFB smears from sputum specimens taken on different days
- An appropriate treatment regimen has been devised and initiated
- Suitable arrangements have been made so that the regimen can be continued and properly monitored on an outpatient basis, specifically by directly observed therapy

3. PATIENTS WHO SHOULD NOT BE DISCHARGED FROM THE HOSPITAL

An individual who is smear positive for AFB should not be directly discharged from the hospital to any of the following:

- A congregate living site (e.g., shelter, nursing home, jail, prison, group home, another hospital)
- A living situation where infants and young children also reside who have not been screened and are not on prophylaxis
- A living situation where immunosuppressed persons (e.g., HIV-infected persons, persons taking cancer chemotherapy) also reside
- A living situation where home health aides or other social service providers will be present in the home for several hours a day to care for the person or family member.

Even after 2 to 3 months of treatment and appearance of negative sputum cultures, some patients with initially positive smears and cultures may continue to excrete what are believed to be dead mycobacteria. Thus, sputum specimens from these patients may be persistently smear positive for AFB and yet culture negative. After their discharge from the hospital, these patients should have weekly sputum smears and cultures until documentation of persistent negative cultures.

VII.B. Return to Work or School

The public health decision of when to allow an individual who is TB Class III or TB Class V to return to work or school is based on three components:

- The characteristics of the individual with TB disease (e.g., whether the individual is likely to adhere to the regimen and follow treatment instructions)
- The characteristics of TB disease itself (e.g., multidrug-resistant vs drug-susceptible TB, AFB smear-positive vs smear-negative, cavitary vs non-cavitary)
- The work environment to which the person will be returning (e.g., working in an AIDS ward vs working alone)

1. PATIENTS KNOWN OR LIKELY TO HAVE DRUG-SUSCEPTIBLE TB

Most Class III or Class V patients known or likely to have drug-susceptible pulmonary TB may be considered for return to certain work settings or school if they meet all three of the following criteria:

- The resolution or near resolution of symptoms, especially cough
- Three consecutive negative AFB smears from sputum specimens taken on different days
- Current treatment with an appropriate anti-TB regimen to which the strain is known or likely to be susceptible

2. PATIENTS WHO GO T0 SCHOOL OR WHO WORK IN CERTAIN SETTINGS

Class III or Class V patients who go to school or who work in a setting where there are persons at increased risk for TB (e.g., worksites where care is provided to HIV-infected persons, neonatal intensive care units, nursing homes, and congregate settings such as prisons, hospitals, shelters, and schools) may be considered for return to these facilities only if they meet all three of the following criteria:

- The resolution or near resolution of symptoms, especially cough
- Three consecutive negative AFB smears from sputum specimens taken on different days
- Current treatment with an appropriate anti-TB regimen to which the strain is known or likely to be susceptible

In addition, patients who work in a health care facility or day care center should not be allowed to return to work until their drug susceptibility results are available.

VII.C. Infection Control in Pulmonary Disease Services Clinic

1. TRIAGE

All individuals entering a Pulmonary Disease Services Clinic for diagnostic evaluation or clinical services should be rapidly assessed for the likelihood that they have infectious TB. As part of this assessment, clinic staff should

- Evaluate the individual for signs and symptoms of infectious TB as soon as he or she enters the clinic

- Search for the individual's name (and unique identifiers) on the TB Patient Index (initial visit only)

    - For infection control purposes, it is important to determine whether the patient has had previous incomplete treatment for TB. Individuals who have been incompletely treated for TB in the past should be suspected of having infectious TB disease (TB Class V), pending the clinical evaluation. Infection control measures should be considered even if the patient does not appear to be symptomatic.

All individuals identified as likely to be infectious must be seen by the physician as quickly as possible. If the physician cannot see the person immediately, the person must be temporarily isolated from others until he or she is seen.

2. MASKS AND PARTICULATE RESPIRATORS

Any individual who is coughing or hoarse should be provided with a mask and instructed to wear it for the duration of the clinic visit. Also, any individual who has been identified as being likely to be infectious by reason of history, the TB patient index, or reported symptoms should be given a mask and instructed to wear it regardless of whether or not he or she is coughing.

- Most masks are acceptable, except those with an escape valve (e.g., type 3M9970).

- Staff should explain the reason for wearing the mask.

- To reduce the patient's discomfort, every effort must be made to limit the amount of time a patient is required to spend in the clinic while wearing a mask.

- Patients who cannot tolerate a mask should be placed in isolation, provided with tissues and instructed to cover their mouth when coughing. All staff must keep a supply of paper tissues readily available in their work areas. Patients not masked should be placed in respiratory isolation and case worker must wear respiratory protection.

- Staff should strongly encourage patients to wash their hands after coughing.

- Signs instructing anyone who is coughing to cover his or her mouth should be prominently displayed in all clinic areas.

Physicians and others attending the masked patient in the consulting room may or may not choose to wear appropriate respiratory protection (e.g., respirator type N95) while the patient is present in the room, but they should consider the following factors:

- If the patient is wearing a mask, and will continue to wear the mask during the consultation, the risk of TB transmission may be reduced. Clinic staff attending the patient are encouraged to wear respiratory protection.

- If the patient is believed to be highly infectious because of his or her history and/or symptomatology, or if the patient is believed to be infected with a drug-resistant TB strain, the risk and consequences of TB transmission may be higher. Clinic staff attending the patient may elect to wear respiratory protection.

- If patient is not wearing a mask, clinic staff must wear respiratory protection.

Staff attending to a patient who is isolated in the sputum induction room must wear appropriate respiratory protection.

3. TEMPORARY ISOLATION

All individuals identified as possibly infectious must be separated from others while awaiting clinical and diagnostic evaluation and/or referral. A sputum induction room or booth (when not in use) is the most appropriate area for temporarily isolating patients awaiting services.

- Staff should carefully explain to isolated patients the reason for their separation.
- Individuals who are temporarily isolated should be instructed to keep their mask on if possible. Individuals who cannot tolerate a mask should be provided with tissues and instructed to cover their mouth when coughing.
- Staff attending to a patient who is isolated in the sputum induction room or isolation waiting room must wear appropriate respiratory protection.
- Clinic staff should frequently check on patients who are being temporarily isolated, to ensure that these patients are comfortable and compliant with isolation protocols.

4. TRANSPORTATION OF PATIENTS

References

1. Centers for Disease Control and Prevention. Guidelines for preventing the transmission of *Mycobacterium tuberculosis* in health-care facilities, 1994. *MMWR* 1994;43 (RR-13):i-132.
2. NIOSH public
3. PDS Respiratory Protection Policy and Procedure.

VIII. Contact Evaluation and Management

Contents

VIII.A. Priorities for Contact Evaluation

Contacts of individuals who have smear- and culture-positive pulmonary or laryngeal TB are much more likely to become infected with *M. tuberculosis* than are contacts of individuals who have smear-negative or culture-negative pulmonary TB. The policy of the Orange County Health Care Agency Pulmonary Disease Services is to assign priority to contact evaluation according to the characteristics of the known or suspected TB index patient and to the characteristics of the contact. In order of priority, a contact should be evaluated if the known or suspected TB index patient has the following characteristics:

1. Sputum smears that are positive for acid-fast bacilli (AFB) (TB Class III or V)

2. Negative AFB smears, but positive *M. tuberculosis* cultures from sputum or laryngeal specimens (TB Class III)

3. Definite clinical evidence of active pulmonary TB, but AFB smears and/or cultures are negative were not obtained prior to the initiation of anti-TB treatment (TB Class III or V)

Additionally, a source case investigation should be performed if a child younger than 5 years old (i.e., up to the day of the fifth birthday) is found to have TB disease or, in certain instances, a positive tuberculin skin test reaction (see Section IX-E). The purpose of the source case investigation is to seek the infectious source patient who infected the child.

Contacts of patients with extrapulmonary TB disease should be evaluated *only if* the patient has concurrent pulmonary or laryngeal TB disease. Contact evaluation is not necessary for patients with extrapulmonary TB disease alone.

VIII.B. Evaluation and Management of Contacts

1. SYMPTOM REVIEW

All close contacts should be evaluated for symptoms of TB. Contacts with TB symptoms have priority over all other contacts.

- Individuals who have symptoms consistent with TB and who have been in close contact with a person who has a positive *M. tuberculosis* culture or an AFB-positive sputum smear should be evaluated promptly for TB disease with a tuberculin skin test, a chest x-ray, and sputum smear, culture, and drug susceptibility testing (see Section IV). If appropriate, there should be a search for extrapulmonary sites of TB.)

- For contacts with definite TB symptoms (e.g., weight loss, a cough of at least 3 weeks duration, fever, night sweats, etc.), with or without an abnormal chest x-ray, treatment for active TB disease should be initiated while TB culture results are pending, unless another cause for such symptoms is likely.

- For contacts with indefinite symptoms, treatment for active TB disease or preventive treatment should be withheld until the diagnostic evaluation is complete. Preventive treatment should not be initiated until active TB disease has been ruled out.

- Contacts with TB symptoms should be classified as TB Class V, regardless of the chest x-ray findings and tuberculin skin test reaction.

2. INITIAL TUBERCULIN SKIN TEST AND FOLLOW-UP

All close contacts of an individual who has a positive *M. tuberculosis* culture or an AFB-positive sputum smear should be screened for TB infection with a tuberculin skin test (TST) and chest x-ray, unless they have documentation of a previous positive TST reaction. Contacts with a documented previous positive reaction should have a chest x-ray.

- If the reaction to the initial TST is negative (<5 mm), the contact should be classified as TB Class I, and a repeat TST should be given 12 weeks after the contact's last exposure to the index patient while he or she was infectious.

  - During the window period between the two TSTs, the following contacts should start preventive treatment, even if TST negative: (1) contacts younger than 5 years old (i.e., up to the day of the fifth birthday); (2) contacts who are HIV seropositive or otherwise immunosuppressed; and (3) contacts with behavioral risk factors for HIV infection who decline HIV testing. These contacts should undergo a chest x-ray to rule out TB disease before starting preventive treatment.

- If the reaction to the initial TST is positive (≥5 mm), the contact should undergo a chest x-ray.

  - If the chest x-ray is normal, the contact should be classified as TB Class II and evaluated for preventive treatment (see Sections III-A, III-B).

  - If the chest x-ray is abnormal, the contact should be classified as TB Class V and evaluated for TB disease (see Section IV).

- In some instances, an individual may present at a Orange County Health Care Agency Pulmonary Disease Services clinic and state that he or she has a positive or negative TST reaction. If it is not possible to verify this information, two options are available: (1) perform a chest x-ray if the person reports a positive TST reaction as well as contact with a person who has TB disease; or (2) repeat the TST, unless the person describes a "very large" reaction (size of a quarter or bigger) to a previous TST or residual evidence (e.g., scar or pigmentation) is seen.

3. REPEAT TUBERCULIN SKIN TEST AND FOLLOW-UP

All contacts with a negative reaction to the initial TST should have a repeat TST 12 weeks after their last exposure to the index patient while he or she was infectious.

- If the reaction to the repeat TST is negative (<5 mm) and the individual is no longer in close contact with an infectious index patient:

  - For immunocompetent contacts (including immunocompetent children), no follow up is necessary. Preventive treatment, if started, should be discontinued. These contacts should be classified as TB Class I.

  - For most close contacts or contacts who are HIV seropositive or have behavioral risk factors for HIV infection but decline HIV testing, a full course of preventive treatment is indicated, regardless of the TST reaction or the results of anergy testing. Anergy testing has no role in the evaluation of contacts (see Section II-F). These contacts should be classified as TB Class II.

- If the reaction to the repeat TST is negative (<5 mm) but the individual remains in close contact with an infectious index patient, the individual should continue preventive treatment if he or she (1) is younger than 5 years old (i.e., up to the day of the fifth birthday); (2) is HIV seropositive or otherwise immunosuppressed; or (3) has behavioral risk factors for HIV infection but declines HIV testing.

- All TST-negative contacts who remain in close contact with an infectious index patient should have a repeat TST and, if necessary, a chest x-ray, every 3 months.

- If the reaction to the repeat TST is positive (≥5 mm), the contact should undergo a chest x-ray (if one has not already been done).

  - If the chest x-ray is normal, the contact should be classified as TB Class II and evaluated for preventive treatment (see Sections III-A, III-B).

  - If the chest x-ray is abnormal, the contact should be classified as TB Class V and evaluated for TB disease (see Section IV).

4. CONTACT EVALUATION FOR PATIENTS WHOSE CULTURES CONVERT BACK TO POSITIVE

In some instances, a TB patient's cultures may convert to negative and then become positive again. This may happen if a patient is lost to follow-up and discontinues his or her medication before completing treatment, or if treatment was not adequate because of multidrug resistance.

- If the patient is found after a treatment lapse of 3 months or longer and his or her cultures have become positive again, or if the patient relapses while on treatment after becoming culture negative, a second window period should be defined and the patient should be re-interviewed.

- Contacts identified during the initial investigation should be reevaluated if they were exposed again.

- If new contacts are identified, they should be tested and evaluated.

VIII.C. Special Considerations for Infant and Child Contacts

An infectious TB patient should be kept out of a home setting where infants and children younger than 5 years old (i.e., up to the day of the fifth birthday) are living until one of the following conditions is met:

- The infectious patient is taking anti-TB treatment and has demonstrated an adequate response to treatment (i.e., negative AFB smears and a decrease in symptoms). This condition applies when there has been one month exposure to the TB case.

- The child has started preventive treatment (including window prophylaxis).

1. INITIAL TUBERCULIN SKIN TEST AND CHEST X-RAY FOR INFANTS

All infant contacts should receive an initial TST and both a posterior-anterior and a lateral chest x-ray.

- If the chest x-rays are normal, the infant should start preventive treatment, even if the TST reaction is negative (<5 mm). Isoniazid preventive treatment should be used for infant contacts of patients with isoniazid-susceptible TB; rifampin should be used for contacts of patients with isoniazid-resistant but rifampin-susceptible TB. Multidrug preventive treatment with medications other than isoniazid and rifampin should be considered for infant contacts of patients with isoniazid- and rifampin-resistant TB (see Section III-C[3]).

  - If the reaction to the initial TST was positive (≥ 5 mm), the infant should complete a full**,** 9-month course of preventive treatment.

- If the reaction to the initial TST was negative (<5 mm), the TST and the posterior-anterior and lateral chest x-rays should be repeated when the infant is 6 months old and 12 weeks have passed since the last exposure to the infectious patient.

- If the chest x-rays show hilar adenopathy (with or without a pulmonary infiltrate), the infant should receive further evaluation. Early-morning gastric aspirates should be collected and treatment should be initiated. Consultation with a pediatric pulmonologist may be indicated to undertake diagnostic investigation for the cause of hilar and/or mediastinal lymphadenopathy.

2. REPEAT TUBERCULIN SKIN TEST AND CHEST X-RAY FOR INFANTS

All infant contacts with a negative reaction to the initial TST should have a repeat TST and posterior-anterior and lateral chest x-rays when they are at least 6 months old and at least 12 weeks have passed since their last exposure to the infectious index patient. (Infants younger than 6 months old may be anergic.)

- If the reaction to the repeat TST is positive (≥5 mm) and the chest x-rays are normal, preventive treatment should be continued, for a total of 12 months of treatment.

- If the reaction to the repeat TST is negative (<5 mm) and the chest x-rays are normal, preventive treatment may be discontinued if the infectious patient is receiving anti-TB treatment and has consistently negative TB cultures. If the infectious patient is culture positive, preventive treatment should be continued until at least 3 months after the patient's cultures convert to negative. Also, if the contact is younger than 6 months old, a full course of preventive treatment should be considered if the source patient is culture negative but has a cavitary chest x-ray.

- If the chest x-rays show hilar adenopathy (with or without a pulmonary infiltrate), the infant should be evaluated with early-morning gastric aspirates and treatment should be initiated, even if the TST reaction is negative (<5 mm).

VIII.D. Contact Investigation for Smear-Negative, Culture-Pending Cases

Pulmonary Disease Services does not routinely evaluate contacts of suspected TB patients (1) whose smears are negative for AFB and whose culture results are pending or (2) whose smear and culture results are pending.
However, certain contacts of these suspected TB patients should be evaluated for TB infection and disease, even if the patient is smear negative:

- Contacts with symptoms of TB. These contacts should be evaluated for TB disease (see Section IV).

- Contacts younger than 5 years old (i.e., up to the day of the fifth birthday). These children should be evaluated with a TST and both a posterior-anterior and a lateral chest x-ray (see Section IX-C).

- HIV-seropositive contacts. It is the policy of the Orange County Health Care Agency Pulmonary Disease Services to perform tuberculin skin testing on all HIV-seropositive individuals, independent of the need to perform a contact evaluation. HIV-seropositive individuals need careful evaluation because of their risk for TB disease.

In addition, a complete contact evaluation may be necessary when the suspected TB case (TB Class V) is reclassified:

- If the suspected TB case is reclassified as a TB Class III on the basis of a positive *M. tuberculosis* culture, a contact evaluation should be performed.

- If the suspected TB case is reclassified as a culture-negative TB Class III, transmission from this index patient may be less likely. Because TST-positive adult contacts may actually have been infected before their exposure to the index patient, preventive treatment may be less imperative. A contact evaluation may not be necessary, but exceptions do occur. A contact evaluation should be performed if, in the opinion of the physician, the index patient was probably infectious at the time of close contact (in spite of negative sputum AFB smears and/or cultures).

- If the suspected TB case is reclassified as Class 0, I, II, or IV, a contact evaluation is not necessary.

VIII.E. Source Case Investigation

All children less than 5 years of age with a positive TST reaction (even in the absence of active TB), should be reported, and a source case investigation should be performed.

The possible source patient is usually an adult in the home, or an adult with whom the child spends significant periods of time (e.g. baby sitters, day care personnel, and relatives).

1. POSSIBLE SOURCE PATIENT WHO IS SYMPTOMATIC

Any possible source patient who has symptoms suggestive of TB should be evaluated for TB disease (see Section IV), including a TST, a chest x-ray, and the collection of three consecutive daily sputum samples for AFB smear, culture, and drug susceptibility testing.

2. POSSIBLE SOURCE PATIENT WHO IS ASYMPTOMATIC

The evaluation and management of an asymptomatic possible source patient depends on his or her HIV status and risk for HIV infection.

If the possible source patient is immunocompetent and not at risk for HIV infection, he or she should be screened with a TST.

- If the TST reaction is <10 mm, the individual should be classified as TB Class 1. No further evaluation is necessary.

- If the TST reaction is ≥10 mm, the individual should undergo a chest x-ray.

    - If the chest x-ray is normal, the individual should be classified as TB Class II. Preventive treatment should be considered if the individual is a candidate for preventive treatment (see Section III-B). Because this individual is not the source patient, the source case investigation should be continued.

    - If the chest x-ray is abnormal, the individual should be classified as TB Class V and evaluated for TB disease (see Section IV).

If the possible source patient (1) is HIV seropositive or otherwise immunosuppressed or (2) has behavioral risk factors for HIV infection but declines HIV testing, he or she should be screened with a TST. In addition, this individual should receive a chest x-ray and a medical evaluation, regardless of the TST reaction. Preventive treatment or treatment for TB disease should be started as appropriate.

Targeted Tuberculin Testing and Treatment of Latent Tuberculosis Infection
Centers for Disease Control & Prevention
http://www.cdc.gov/mmwr/preview/mmwrhtml/rr4906a1.htm
MMWR; Vol. 49/No. RR-6

Treatment of Tuberculosis and Tuberculosis Infection in Adults and Children
http://www.thoracic.org/adobe/statements/tbchild1-16.pdf
American Thoracic Society